Antiseizure Drugs and Pharmacological Management of Parkinsonism and Other Movement Disorders

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Antiepileptic Drugs
(AED)

Anticonvulsants

Terminology

- **Seizure**
- **Fit**
- **Spell**
- **Convulsion**
- **Epileptic seizure**
- **Epilepsy**

Nature of Epilepsy

- Epilepsy affects about 0.5% of the population.
- The characteristic event is the seizure, which is often associated with convulsion, but may occur in many other forms.
- The seizure is caused by an abnormal high-frequency discharge of a group of neurons, starting locally and spreading to a varying extent to affect other parts of the brain.

Nature of Epilepsy

- Seizures may be partial or generalized depending on the location and spread of the abnormal neuronal discharge. The attack may involve mainly motor, sensory or behavioral phenomena. Unconsciousness occurs when the reticular formation is involved.

Types of Epilepsy

- **Two major categories, *partial* and *generalized* seizures.**

Partial seizures

- **The discharge begins locally, and often remains localized. Produce relatively simple symptoms without loss of consciousness.**

Generalized seizures

- **Involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. Immediate loss of consciousness.**

Table 24–1. Classification of seizure types.

Partial seizures	
	Simple partial seizures
	Complex partial seizures
	Partial seizures secondarily generalized
Generalized seizures	
	Generalized tonic-clonic (grand mal) seizures
	Absence (petit mal) seizures
	Tonic seizures
	Atonic seizures
	Clonic and myoclonic seizures
	Infantile spasms[1]

[1]An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.

Nature of Epilepsy

- Two common forms of generalized epilepsy are the tonic-clonic convulsion or fit (grand mal) and the absence seizure (petit mal).
- Status epilepticus is a life-threatening condition in which seizure activity is uninterrupted.

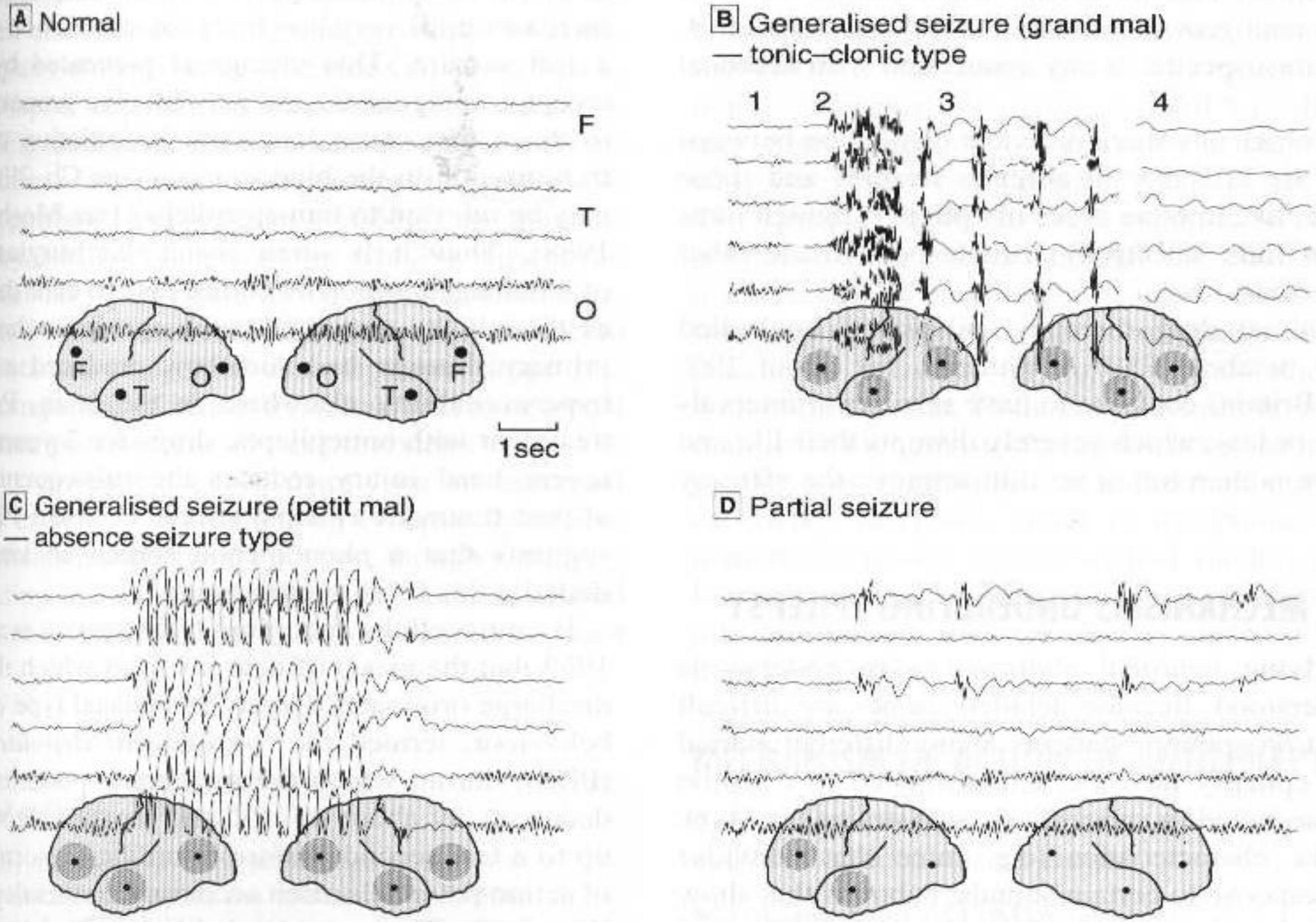


Fig. 36.1 EEG records in epilepsy. A Normal EEG recorded from frontal (F), temporal (T) and occipital (O) sites on both sides, as shown in the inset diagram. The α-rhythm (10/s) can be seen in the occipital region. B Sections of EEG recorded during a generalised tonic–clonic (grand mal) seizure. 1. Normal record. 2. Onset of tonic phase. 3. Clonic phase. 4. Post-convulsive coma. C Generalised absence seizure (petit mal) showing sudden brief episode of 3/s 'spike and wave' discharge. D Partial seizure with synchronous abnormal discharges in left frontal and temporal regions. (From: Eliasson S G et al. 1978 Neurological pathophysiology, 2nd edn. Oxford University Press, New York)

Nature of Epilepsy

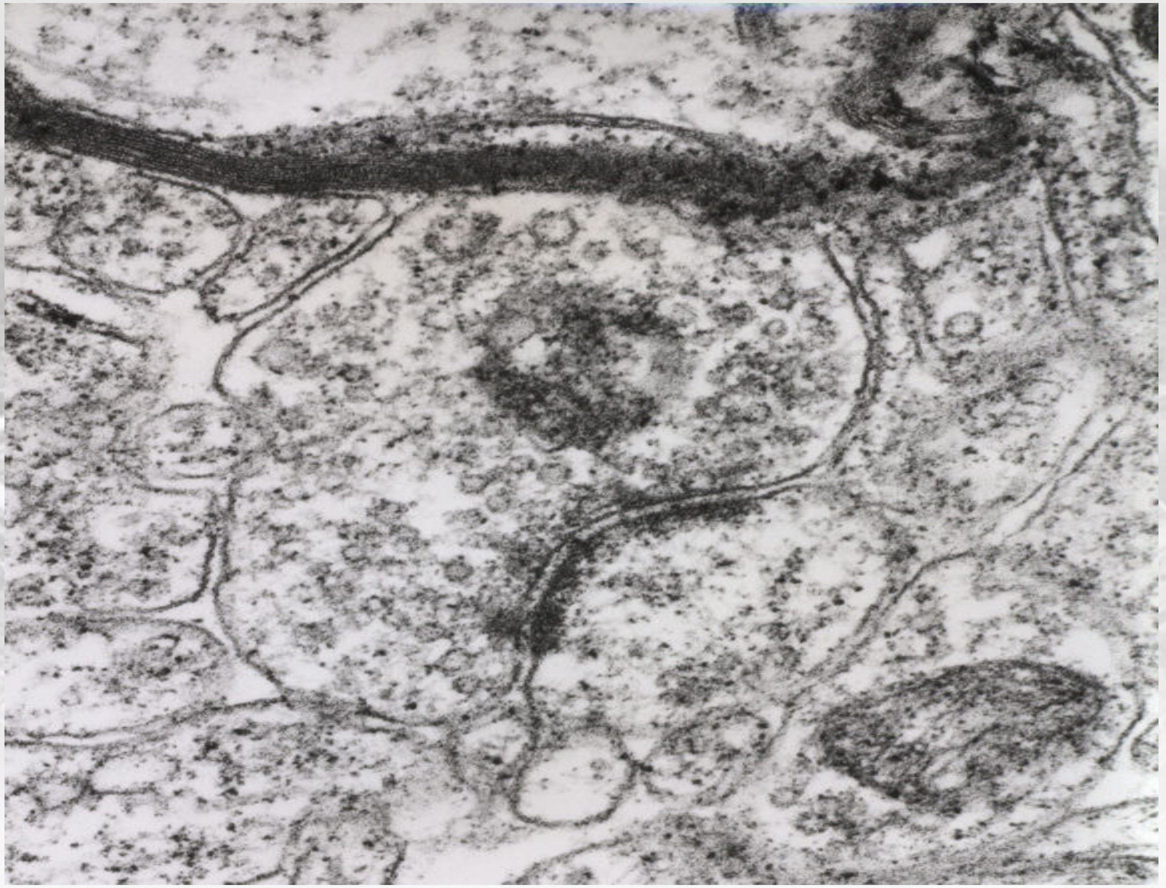
- **Repeated epileptic discharge can cause neuronal death (excitotoxicity).**
- **Current drug therapy is effective in 70-80% of patients.**

Overview

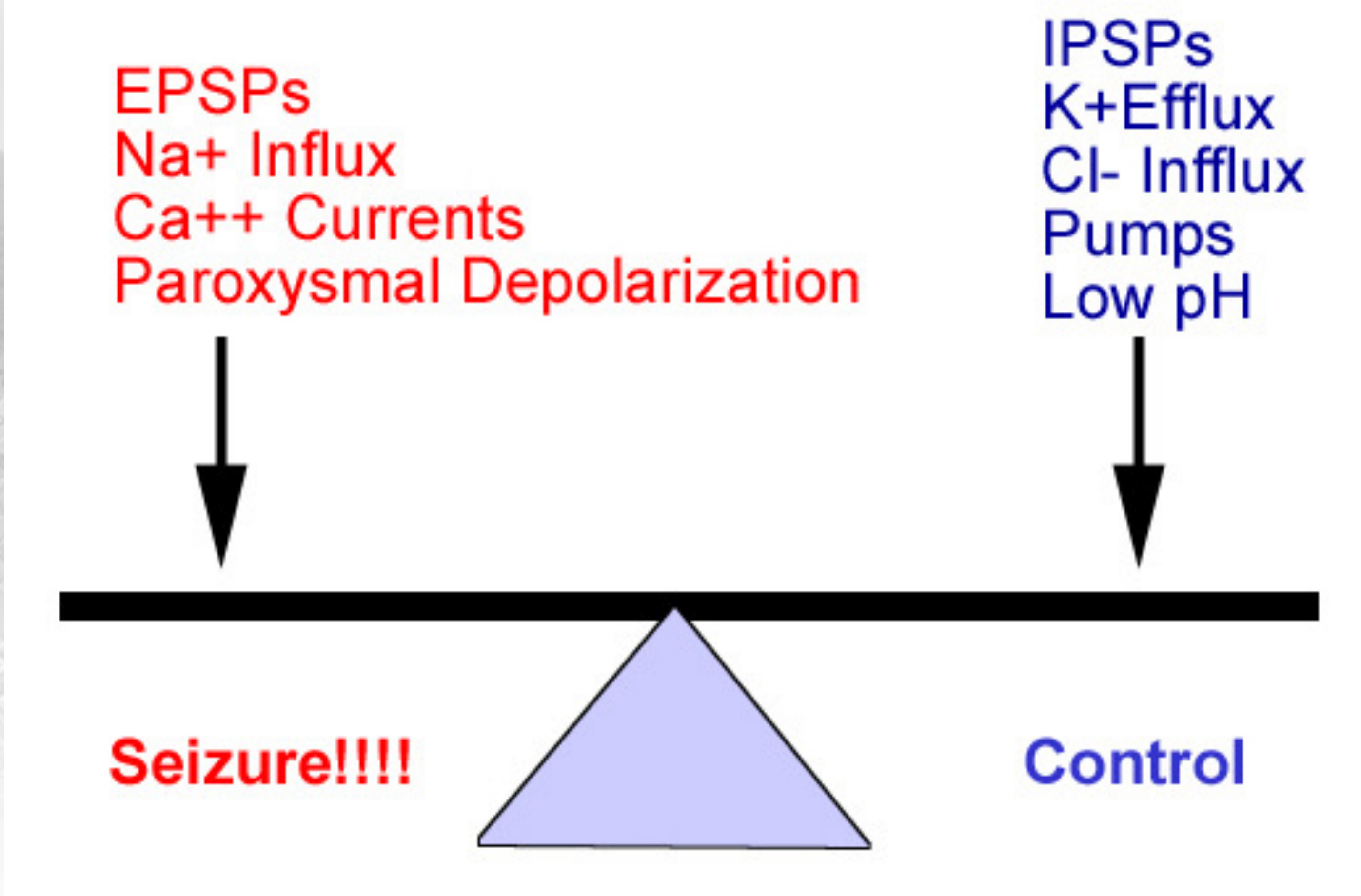
- 1850, Bromides.
- 1910, Phenobarbital.
  - primidone.
- 1938, Houston Merrit and Tracy Putnam introduced animal models.
- 1940 Phenytoin (PHT)
- 1968 carbamazepine (CBZ) for trigeminal neuralgia; in 1974, it was approved for partial seizures.
- 1958, Ethosuximide as a first-choice drug for the treatment of absence seizures without generalized tonic-clonic seizures.
- 1960, Valproate in Europe and 1978 in the United States. It became the drug of choice in primary generalized epilepsies and in the mid 1990s was approved for treatment of partial seizures.
- 1990s, newer AEDs with good efficacy, fewer toxic effects, better tolerability, and no need for blood level monitoring.

Mechanism of Action

- ***Current antiepileptic drugs are thought to act mainly by two main mechanisms:***



The dynamic target of seizure control in the management of epilepsy is achieving balance between the factors that influence the excitatory postsynaptic potential (EPSP) and those that influence inhibitory postsynaptic potential (IPSP)



Mechanism of Action

- Reducing electrical excitability of cell membranes, possibly through inhibition of sodium channel.

- Enhancing GABA-mediated synaptic inhibition. This may be achieved by an enhanced pre- or post- synaptic action of GABA, by inhibiting GABA-transaminase, or by drugs with direct GABA-agonist properties.

Mechanism of Action

- **A few drugs appear to act by a third mechanism, namely inhibition of T-type calcium channels.**
- **Newer drugs act by other mechanism, yet to be elucidated.**
- **Drugs that block excitatory amino acid receptors are effective in animal models, but not yet developed for clinical use.**

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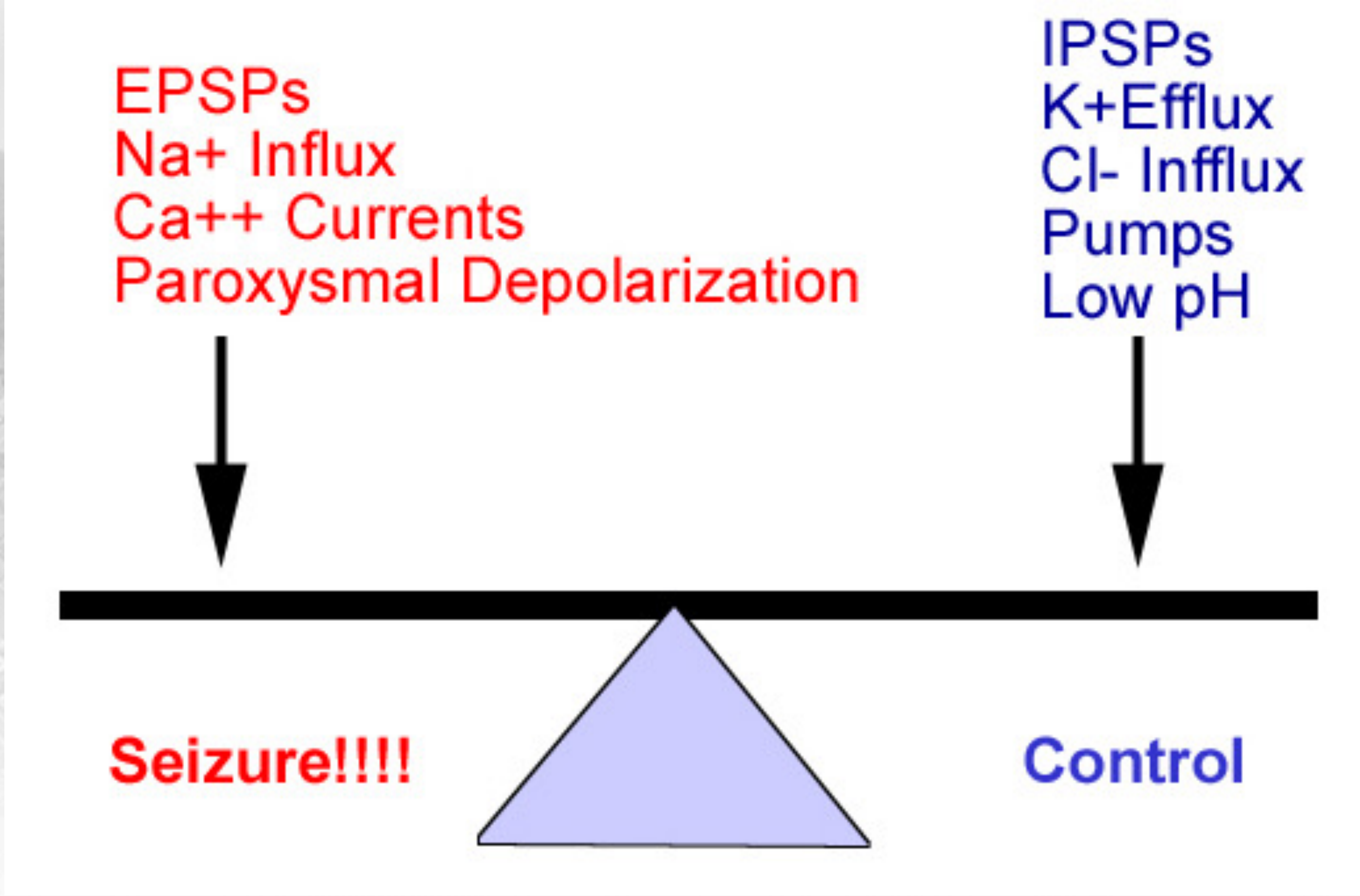
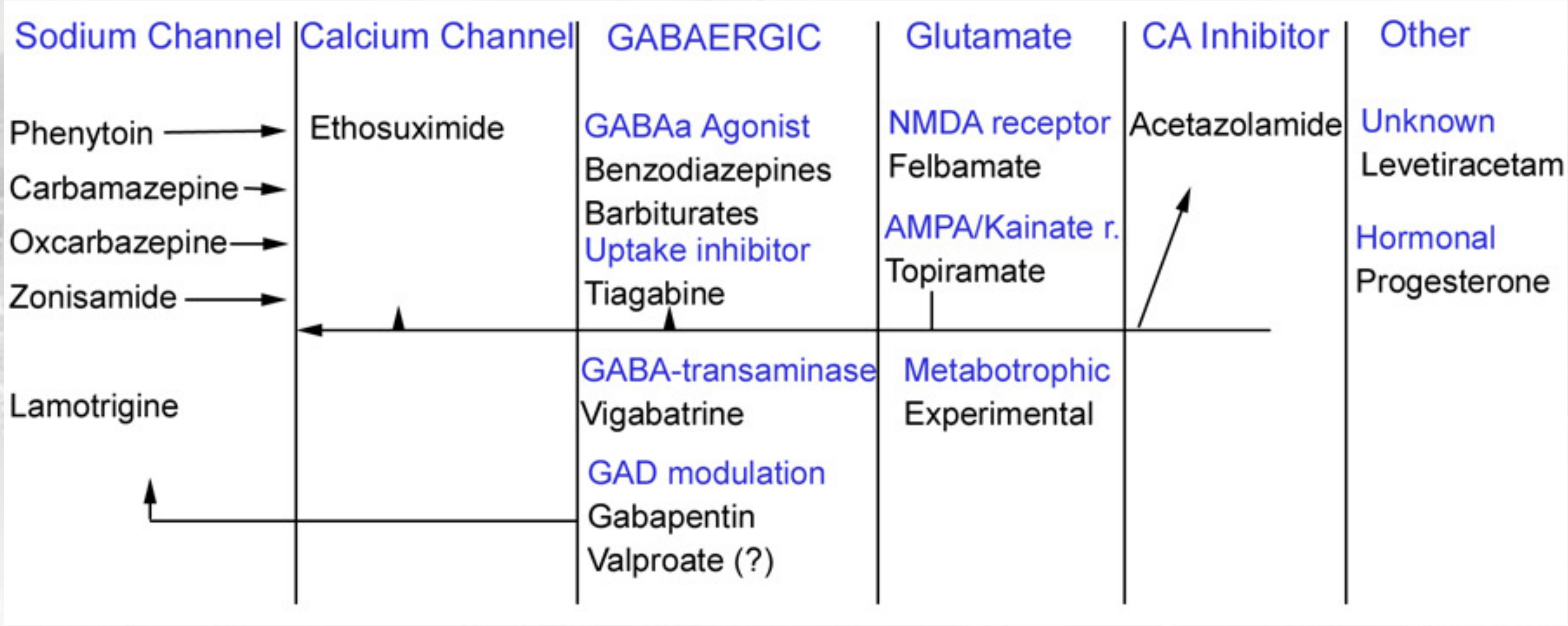
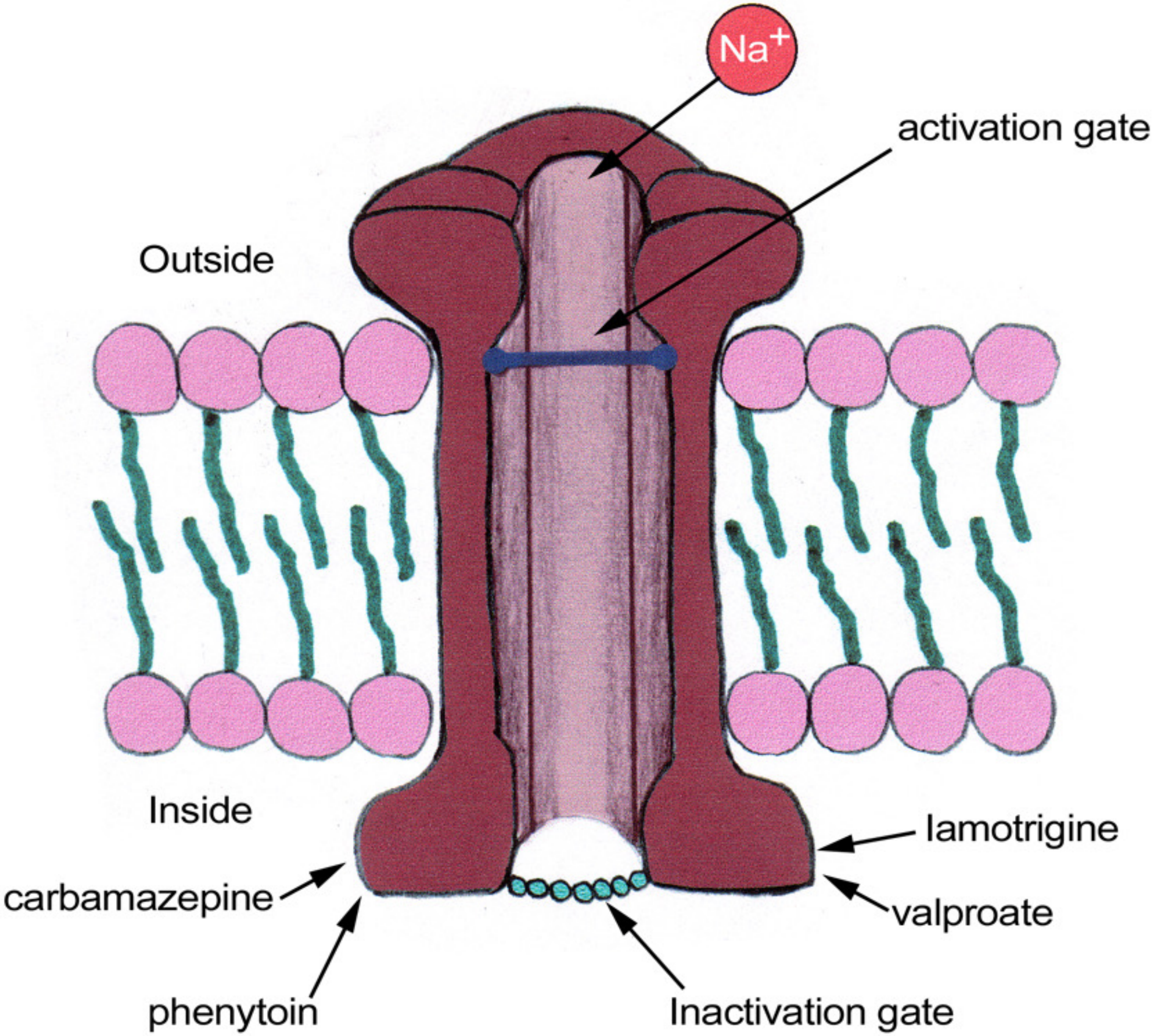


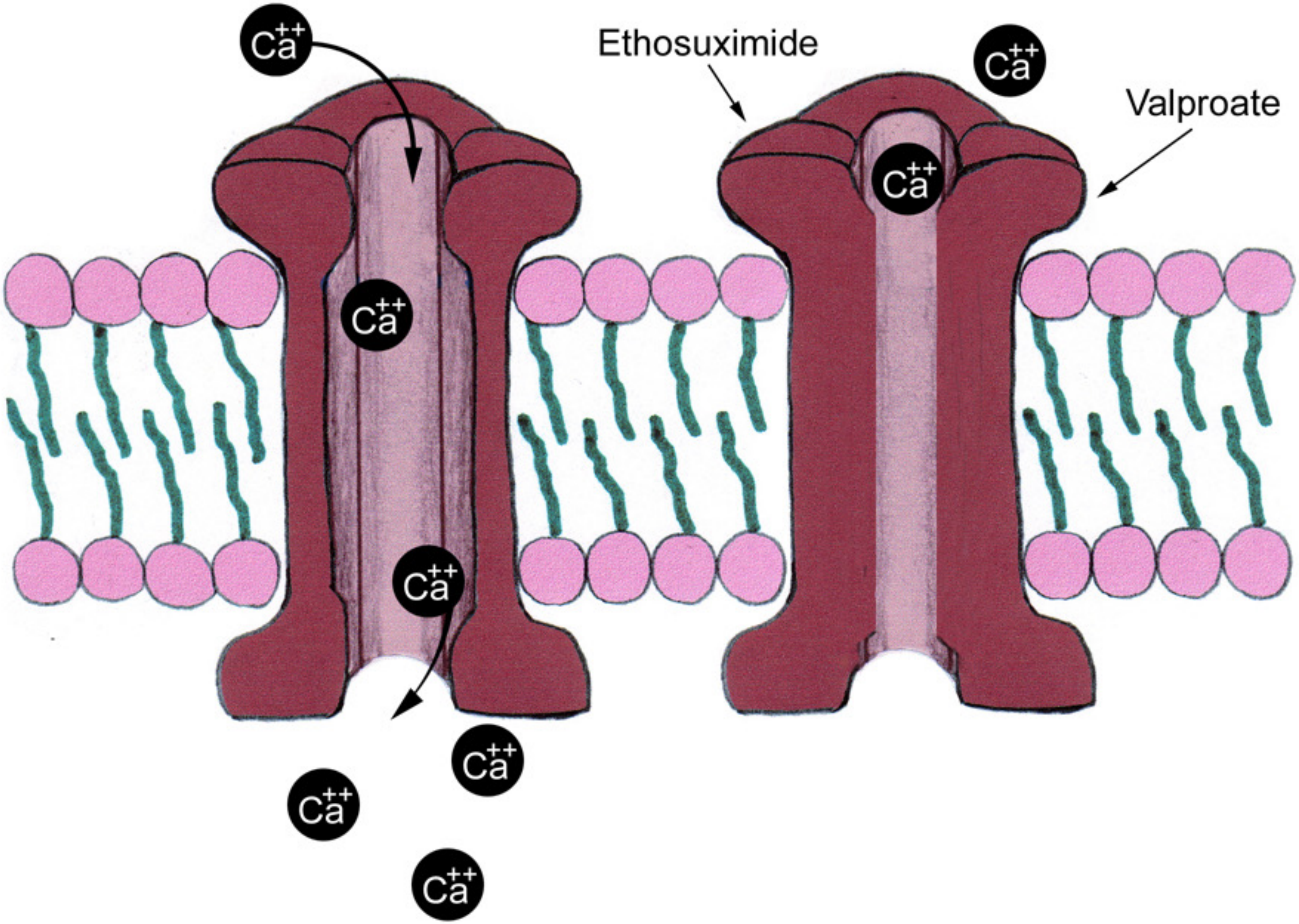
Antiepileptic drugs can be grouped according to their major mechanism of action. Some antiepileptic drugs work by acting on a combination of channels and/or some unknown mechanism of action.



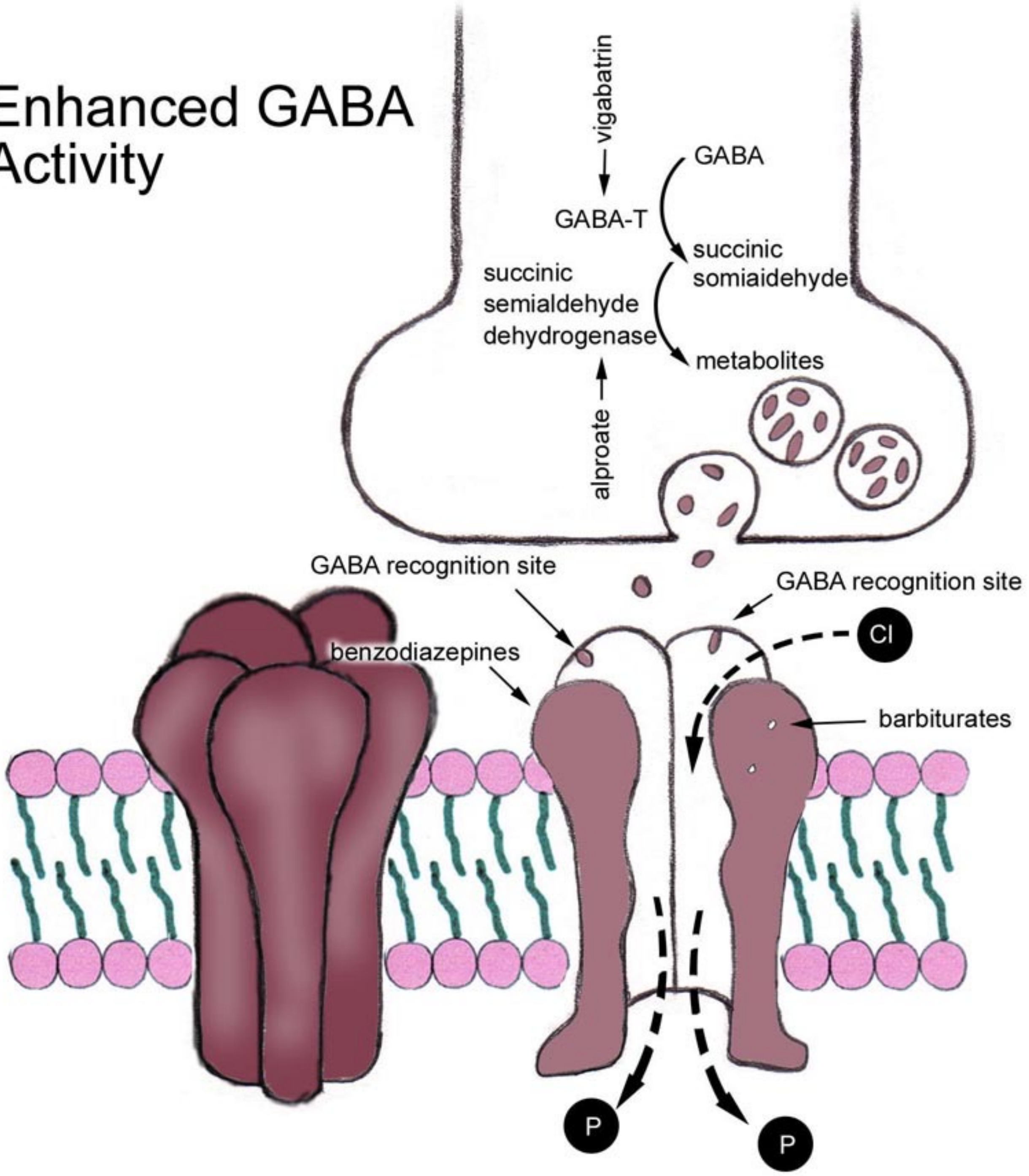
Enhanced Na^+ Channel Inactivation



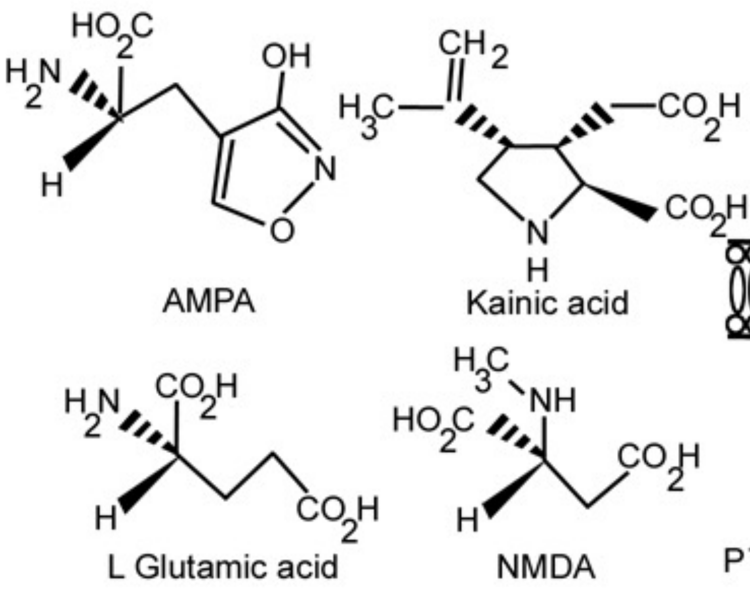
Reduced Current through T-Type Calcium Channels



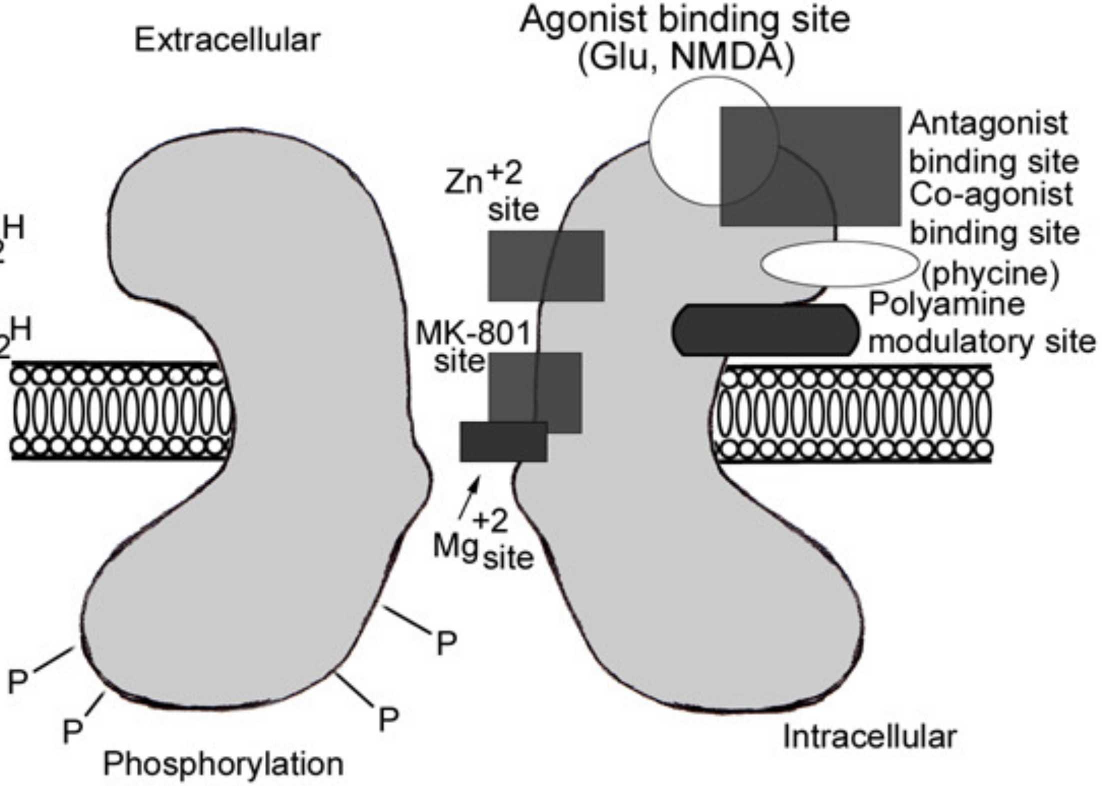
Enhanced GABA Activity



NMDA	AMPA/KAINATE	METABOTROPHIC
Felbamate Levetiracetam (glycine?)	Tropiramate	Under research

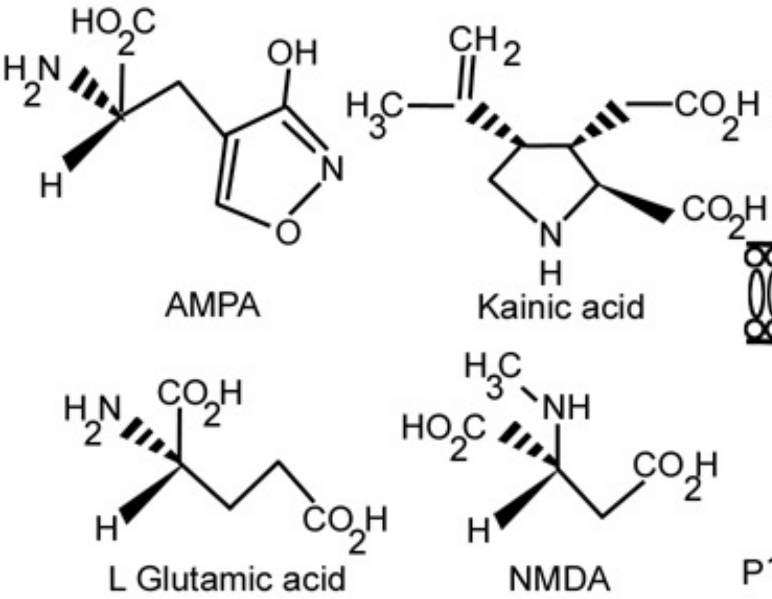


Glutamate receptor agonists:
1-Glutamic acid; AMPA ((s)-a-amino-3-hydroxy-5-methyl-1-4 isoxazolepropionic acid); Kainic acid; and NMDA (*N*-methyl D-aspartic acid).



Schematic representation of the NMDA receptor.

$GABA_A$ agonist	UPTAKE BLOCKER	GABA-T INHIBITOR	GAD modulator?	PRODRUG
Barbiturates Benzodiazepines Progesterone Ganaloxone	Tiagabine	Vigabatrine	Gabapentin Valproate	Progabide



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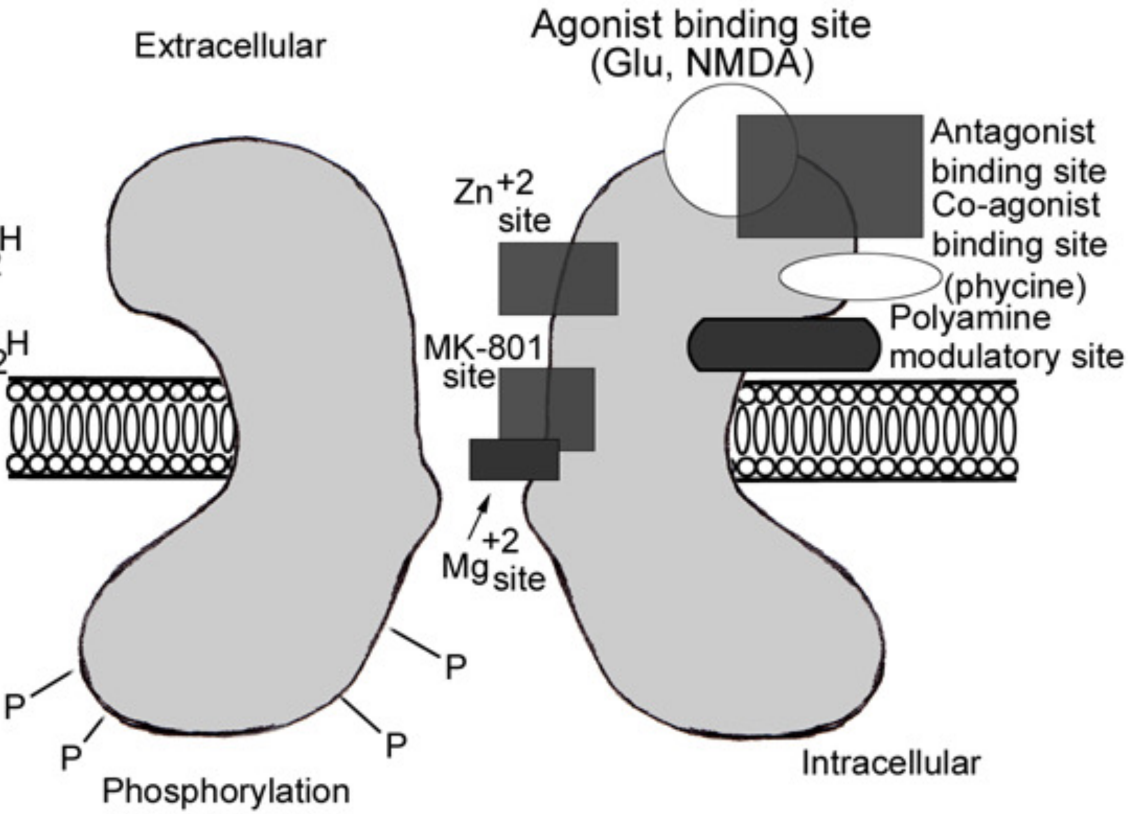

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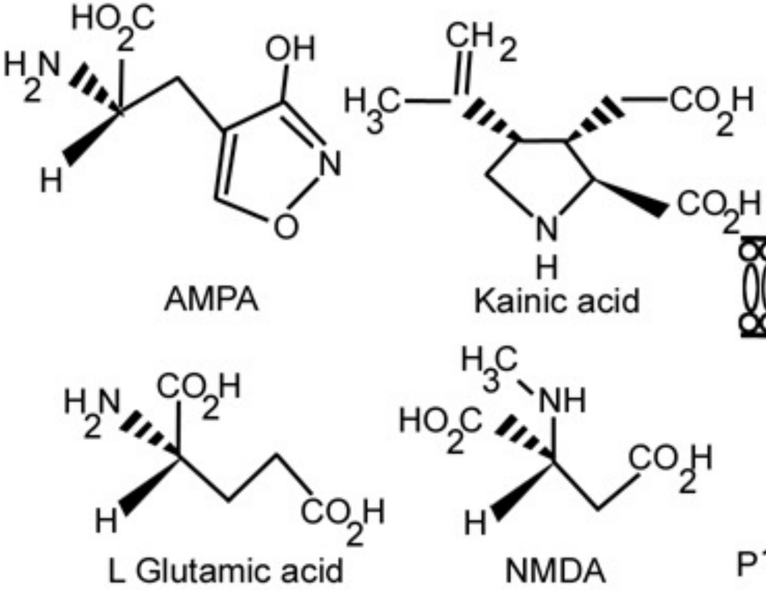

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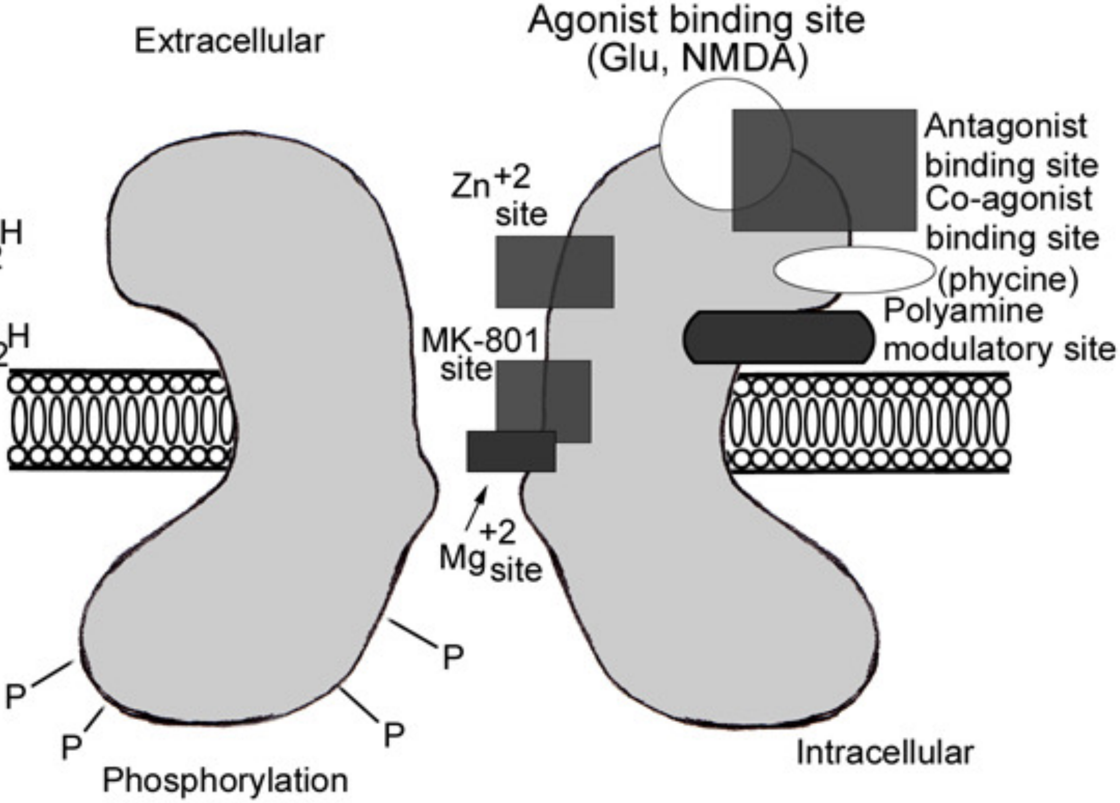


Schematic representation of the NMDA receptor.

The Major Antiepileptic Drugs

- The main drugs in current use are: phenytoin, carbamazepine, valproate and ethosuximide.
- Secondary drugs include:
  - Phenobarbitone: highly sedative
  - Various benzodiazepines (e.g. clonazepam);

  Diazepam used in treating status epilepticus.

Phenytoin

Mechanism of Action: acts by stabilizing membranes

(1) Blocking voltage-dependence Na^{+} channel

(2) Blocking voltage-dependence Ca^{2+} channel

(3) Inhibiting calcium-induced secretory processes, including release of hormones and neurotransmitters.

(4) Inhibiting post tetanic potentiation (PTP).

PHARMACOKINETICS

- **Because phentoin is a weak acid, its intestinal absorption is variable and plasma concentration can vary widely. Monitoring is therefore needed**
- **It is metabolized by the microsomal system and is excreted first in the bile and then in the urine.**

Therapeutic uses

- **Antiseizure: used in the treatment of grand mal epilepsy and tonic-clonic seizure disorders, not in absence seizures.**
- **Treatment on peripheral neuralgia .**
- **Antiarrhythmias**

Adverse effects

- **Gastrointestinal irritation**
- **Ataxia and diplopia.**
- **Blood dyscrasias.**
- **Gingival hyperplasia, hirsutism, increased collagen proliferation.**

Adverse effects

- **Hepatitis.**
- **Fetal malformations: fetal hydantion syndrome**
- **Drug interactions: increased plasma concentrations of phenytoin can occur by concurrent administration of chloramphenicol, isoniazid, cimetidine, dicumarol, et al.**

Carbamazepine

- Derivative of tricyclic antidepressants
- Similar profile to that of phenytoin, but with fewer unwanted effects
- Effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy; also useful in trigeminal neuralgia and mania.

Carbamazepine

- **Strong inducing agent; therefore many drug interactions**
- **Low incidence of unwanted effects; principally sedation, ataxia, mental disturbances, water retention**

Valproate

- **Valproate is very effective against absence seizure.**
- **Mechanism: facilitate glutamic acid decarboxylase; inhibit GABA-transaminase; enhance synaptic responses. some effect on sodium channels**
- **Relatively few unwanted effects: anorexia, nausea, teratogenicity, liver damage (rare, but serious)**

Ethosuximide

- The main drug used to treat absence seizures, may exacerbate other forms
- Acts by blocking T-type Ca^{2+}-channels
- Relatively few unwanted effects, mainly nausea and anorexia. (mental disturbances)

Benzodiazepine

- **Diazepam: preferred drugs for Status epilepticus.**
- **Nitrazepam: petit mal ,especially myoclonic seizures and infantile spasms.**
- **Clonazepam: is one of the most effective in some cases of myoclonic seizures. Used in petit mal and status epilepticus**

Barbiturates

- Phenobarbital, Luminal: is useful in the treatment of generalized tonic-clonic seizures and statue epilepticus.
- Mechanism:(1) block Ca^{2+} currents presynaptic membrane and decrease neurotransmitter release.(2) prolong the openings of the Cl^{-} channel in postsynaptic membrane and decrease it’s response.
- Adverse effects: sedation, depression, drug interaction.

Newer Antiepileptic Drugs
(Second- Generation)

Newer Antiepileptic Drugs (Second- Generation)

1. **Vigabatrin 1989**
2. **Gabapentin 1993****
3. **Lamotrigine 1994****
4. **Topiramate 1996****
5. **Tiagabine 1997**
6. **Levetiracetam 1999**
7. **Oxcarbazepine 2000** (safety profile similar to CBZ). Hyponatremia is also problem, however it is less likely to cause rash than CBZ.
8. **Zonisamide 2000**

- **NEWER AGENTS DIFFER FROM OLDER DRUGS BY**

Relatively lack of drug-drug interaction (simple pharmacokinetic profile) Improved tolerability

HOWEVER THEY ARE

Costly with limited clinical experience

Lamotrigine

Pharmacological effects

Resembles phenytoin in its pharmacological effects

Well absorbed from GIT

Metabolised primarily by glucuronidation

Does not induce or inhibit C. P-450 isozymes (its metabolism is inhibitted by valproate)

Plasma t 1/2 approx. 24 hrs.

- **Mechanism of Action:**

Inhibits excitatory amino acid release (glutamate & aspartate) by blockade of Na channels.

- **Uses:** As add-on therapy or as monotherapy
- **Side effects:**
- Skin rash, somnolence, blurred vision, diplopia, ataxia, headache, aggression, influenza – like syndrome

Gabapentin

- Structural analogue of GABA .May increase the activity of GABA or inhibits its re-uptake.

Pharmacokinetics:

Not bound to proteins

Not metabolized and excreted unchanged in urine

- Does not induce or inhibit hepatic enzymes (similar to lamotrigine)
- Plasma $t_{1/2}$ 5-7 hours
- **Side effects:**
- Somnolence, dizziness, ataxia, fatigue and nystagmus.
- **Uses:**
- As an adjunct with other antiepileptics

Topiramate

Pharmacological Effects:

- Well absorbed orally (80 %)
- Food has no effect on absorption
- Has no effect on microsomal enzymes
- 9-17 % protein bound (minimal)
- Mostly excreted unchanged in urine
- Plasma t1l2 18-24 hrs

Mechanism of Action:

- Blocks sodium channels (membrane stabilization) and also potentiates the inhibitory effect of GABA.

Topiramate (Cont.)

Clinical Uses:

- Recently, this drug become one of the safest antiepileptics which can be used alone for partial and generalized tonic-clonic, and absence seizures.

Side effects:

- Psychological or cognitive dysfunction
- Weight loss
- Sedation
- Dizziness
- Fatigue
- Urolithiasis
- Paresthesias (abnormal sensation)
- Teratogenecity (in animal but not in human)

Vigabatrin (restricted)

Pharmacological effects: Drug of choice for infantile spasms

- Not bound to proteins ,Not metabolized and excreted unchanged in urine
- Plasma t1/2 4-7 hrs

Mechanism of action :

Inhibits GABA metabolizing enzyme & increase GABA content in the brain(similar to valproate).

Side effects:

Visual field defects, psychosis and depression (limits its use).

Zonisamide

Pharmacokinetics:

- Well absorbed from GIT (100 %)
- Protein binding 40%
- Extensively metabolized in the liver
- No effect on liver enzymes
- Plasma $t_{1/2}$ 50 -68 hrs

Clinical Uses:

Add-on therapy for partial seizures

Side Effects:

Drowsiness, ataxia , headache, loss of appetite,nausea& vomiting, Somnolence .

Tiagabine

- Adjunctive therapy in partial and generalized tonic-clonic seizures

Pharmacological effects

- Bioavailability > 90 %
- Highly protein bound (96%)
- Metabolized in the liver
- Plasma t ½ 4 -7 hrs

Mode of action:

- inhibits GABA uptake and increases its level

Tiagabine cont'd

Side effects:

- Asthenia
- Sedation
- Dizziness
- Mild memory impairment
- Abdominal pain

Levetiracetam

- **Levetiracetam (LEV) - a piracetam (S-enantiomer pyrrolidone) derivative.**
- **To enhance cognitive functions and for anxiolysis in the 1980s.**
- It is **a unique AED** in that it is ineffective in classic seizure models that screen potential compounds for antiseizure efficacy such as maximal electroshock and pentylenetetrazol in rats and mice. During preclinical evaluations, it was found to be effective in several models of seizures, including tonic and clonic audiogenic seizures in mice, tonic seizures in the maximum electroshock-seizure test in mice, and tonic seizures induced in rodents by chemoconvulsants.

Levetiracetam

Pharmacokinetics:

- LEV is absorbed rapidly following oral administration, with an oral bioavailability of approximately 100%.
- Peak concentration approximately 0.6-1.3 hours, not bind to plasma proteins.
- It does not involve the enzymes of the cytochrome P-450 system.
- Approximately 66% is excreted unchanged in urine.
- Elimination half-life is only 6-8 hours

Levetiracetam

- **Adverse effects** were reported in more than 10% of cases.
  - They included headache (25%),
  - Accidental injury (25%),
  - Convulsion (23%),
  - Infection (23%),
  - Asthenia (22%),
  - Somnolence (22%),
  - Dizziness (18%), Pain (15%), Pharyngitis (11%), and a Flu-like syndrome (10%).

Levetiracetam

- **LEV is very useful in patients with hepatic or renal insufficiency and patients on concomitant medications, because it has no drug interactions. Current data support a good safety profile and efficacy in different patient populations, causing LEV to become one of the preferred AEDs in elderly patients.**

Clinical Advices for the Use of Drugs in the Treatment of Epilepsy

General features:

- ***It is essential to have an accurate and comprehensive diagnosis.***
- ***Must treat underlying causes e.g. hypoglycemia , infection and tumor***
- ***Diagnosis: Adequate description of symptoms both from patient and eye witness.***
- *EEG should not be an indication for confirming epilepsy nor to stop treatment for seizure free patients.*

Common Causes of Failure of Antiepileptics

1. Improper diagnosis of the type of seizures
2. Incorrrect choice of drug
3. Inadequate or excessive dosage
4. Poor compliance

Antiepeliptics and Pregnany:

- Seizure very harmful for pregnant women.
- Monotherapy usually better than drugs combination.
- Folic acid is recommended to be given for every pregnant women with epilepsy
- Phenytoin, sodium valproate are absolutely contraindicated and oxcarbamazepine is better than carbamazepine.
- Experience with new anticonvulsants still not reliable to say that are better than old ones.

Possible Mechanism of Action

1) By acting on the neuronal membrane action potential:

- **Membrane Stabilization: Phenytoin; Carbamazepine: Phenobarb; Lamotrigine; Topiramate, Zonisamide.**
- **Prolong refractory period: e.g: Ethosuximide; Valproate**

2) By inhancement of GABA neurotransmissions:

- **Inhibit GABA catabolism (inhibit GABA transaminase) e.g: Valproate; Vigabatrin**
- **Inhibit re-uptake of GABA: benzodiazepines**
- **Analog of GABA: e.g: Gababentin**
- **Increase the activity of GABA: phenobarbitone; Topiramate; Gabapentin**

3) By antagonizing the action of Aspartate and Glutamate **e.g: Lamotrigine**

Clinical Uses of Antiepileptic Drugs

- *Tonic-clonic (grand mal)* **seizures:** carbamazepine **preferred because of low incidence of side-effects,** phenytoin, valproate. **Use of single drug is preferred when possible, because of risk of pharmacokinetic interactions.**
- *Partial (focal)* **seizures:** carbamazepine, valproate; clonazepam **or** phenytoin **are alternatives.**

Clinical Uses of Antiepileptic Drugs

- ***Absence seizures (petit mal)*:** ethosuximide **or** valproate**. Valproate is used when absence seizures coexist with tonic-clonic seizures, since most drugs used for tonic-clonic seizures may worsen absence seizures.**
- ***Myoclonic seizures*:** valproate **or** clonazepam**.**
- ***Status epilepticus*: must be treated as an emergency, with diazepam intravenously.**

Attentions

- Selection of an appropriate antiepileptic agent
- Use of single drug (monotherapy)
- Withdrawal
- Toxicity
- Fetal malformations

Pearls of antiepileptic drug use and management

HEPATIC ENZYME INDUCERS

PHENYTOIN
CARBAMAZEPINE (also autoinduction)
BARBITURATES
OXCARBAZEPINE
TOPIRAMATE (weak)

MAINLY RENALLY EXCRETED

GABAPENTIN
LEVETIRACETAM
TOPIRAMATE (lesser extend)

CONCOMITANT MIGRAINE

VALPROATE
GABAPENTIN
TOPIRAMATE

WEIGHT LOSS

TOPIRAMATE
ZONISAMIDE

PARENTERAL AVAILABLE

PHENYTOIN/FOSPHENYTOIN
VALPROATE
BARBITURATES
BENZODIAZEPINES

ONCE DAILY DOSE

PHENYTOIN
ZONISAMIDE
VALPROATE
PHENOBARBITAL

HIGH PROTEIN BINDING

PHENYTOIN	(70-90%)
VALPROATE	(85-95%)
TIAGABINE	(96%)
CARBAMAZEPINE	(75%)
CLOBAMAZEPINE/CLONAZEPAM	(83%-86%)
PHENOBARBITAL	(45%-60%)

ACTIVE METABOLITIES

CARBAMAZEPINE	EPOXIDE
CLOBAZAM	N-DESMETHYLCLOBAZAM
OXCARBAZEPINE	10-MONOHYDROXY (MHD)
PRIMIDONE	PHENOBARNITAL

AVOID IN YOUNG WOMEN

VALPROATE	higher teratogenic risk
PHENYTOIN	cosmetic effects, hirutism

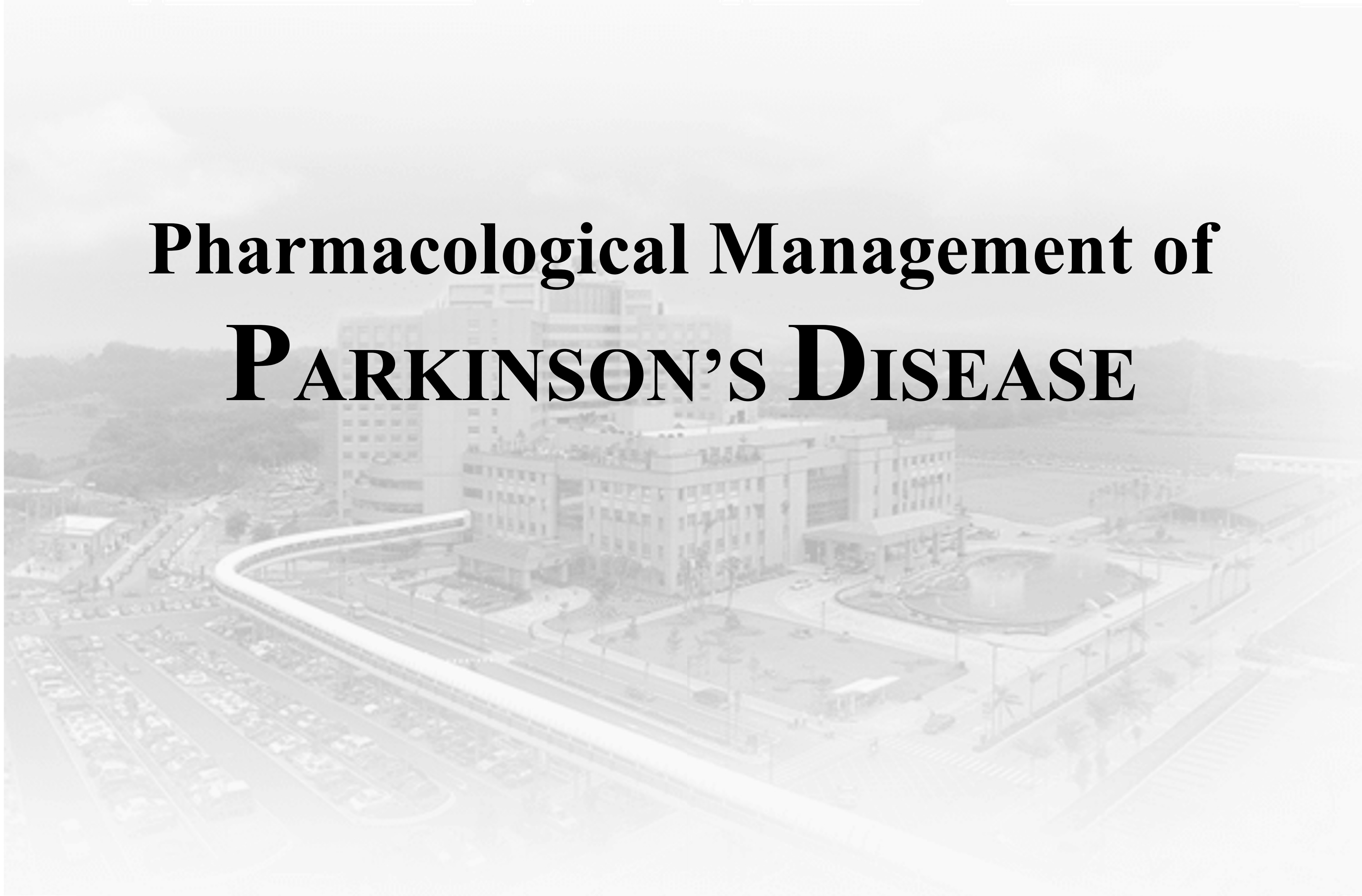
MANAGEMENT OF CLUSTER SEIZURES

LORAZEPAM PERORALLY	0.03-0.05mg/Kg
RECTAL DIAZEPAM GEL	0.2-0.5mg/Kg

Pharmacological Management of Parkinsonism and Other Movement Disorders

張振聲醫師

Pharmacological Management of
PARKINSON'S DISEASE



PARKINSONISM

A Symptom Complex of

- **Tremor**
- **Rigidity**
- **Akinesia**
- **Postural instability**

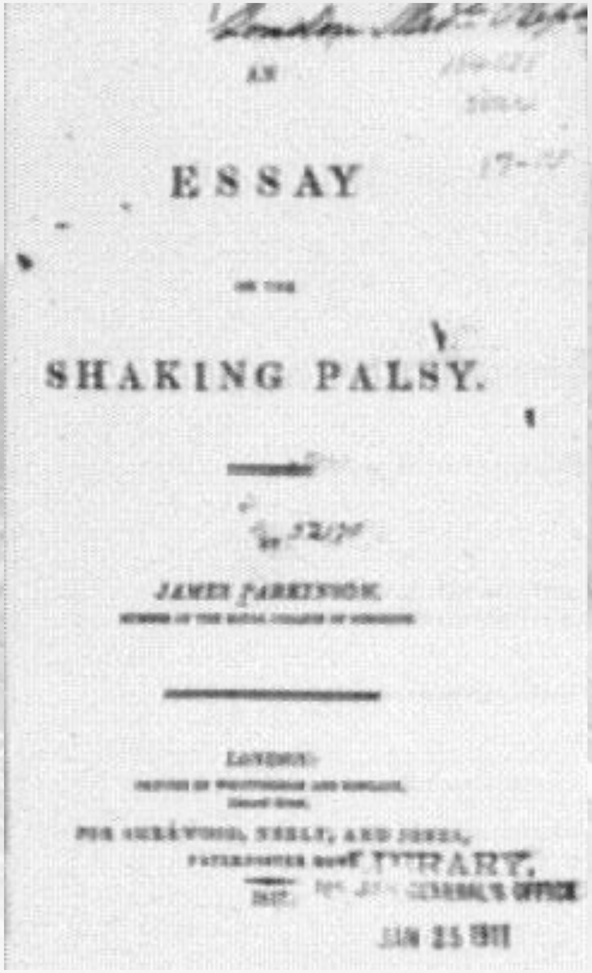
- **Parkinsonism**
- **Parkinsonian syndrome**
- **Akineto-rigid syndrome**
- **Idiopathic parkinsonism**
  - **Parkinson’s disease**

PARKINSON'S DISEASE

Clinical Features/Cardinal Signs

- **Diagnosis requires 2 of 3:**
  - **Bradykinesia; rigidity; tremor (primarily at rest)**
- **Other signs: Masked face, hypovolemic speech, swallowing difficulty, micrographia, fixed posture, shuffling gait, start hesitancy and freezing**
- **Onset: Insidious, unilateral progressing to bilateral**

Dr. James Parkinson (1755 - 1824)



- Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.

巴金森氏病

- 發病年齡 ：
  - 平均大約 55至60 歲左右
  - 50 至 60 歲約佔 40%
  - 40 歲以下 10%
- 發生率 ：
  - 大約 1-2/1000人
  - 65(或60)歲以上 ：1/100 人

Possible Risk Factors for PD

- Male gender
- Caucasian
- Genetic predisposition
- Rural living
- Drinking well water
- Farming
- Industrial chemical exposure
- Herbicide/pesticide exposure

ETIOLOGY OF PD

- **Heredity**
- **Toxicity**
- **Aging**
- **Oxidative Stress as a Determinant of Neuronal Loss**

ETIOLOGY OF PD

- **A combination of toxic factors, either endogenous or exogenous, acting on a predisposed individual having inherited a varying degree of genetic susceptibility. Through different pathways these factors would lead to neuronal loss, probably determined by either energy failure or oxidative stress.**

巴金森氏病的症狀

- 主要運動症狀(巴金森氏症候):
  - 顫抖
  - 僵硬
  - 無動症，寡動症，緩動症(動作遲緩)
  - 姿勢不穩
- 其他次要症狀: 張力異常症，自主神經功能異常，憂鬱症，疼痛和痲痺感覺症狀等 。

病情程度的分級

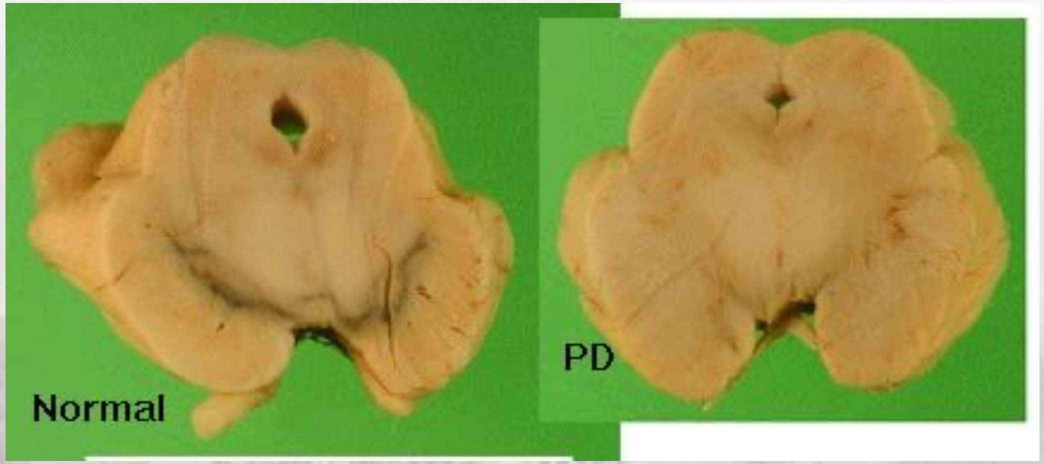
(Hoehn and Yahr 分級）

1. 第一級：單側顫抖，僵硬，無動症症狀
2. 第二級：兩側顫抖，僵硬，無動症症狀
3. 第三級：兩側症狀，併姿勢不穩但仍可自行生活
4. 第四級：症狀明顯，日常生活需要別人照顧，無法自行生活
5. 第五級：終日臥床或坐輪椅，完全需人幫助

巴金森氏病的病程

- 巴金森氏病為一漸進性之退化疾病, 臨床上依病人行動障礙可分成五級：
  - 第一級：單側肢體發生巴金森症，對生活幾無影響。
  - 第二級：雙側均有問題，平衡正常。
  - 第三級：無法維持穩定的姿勢，例如轉身時步態不穩。
  - 第四級：病人可站立或行走，但有嚴重活動困難。
  - 第五級：病人臥床或困坐輪椅，必須旁人照料其生活。

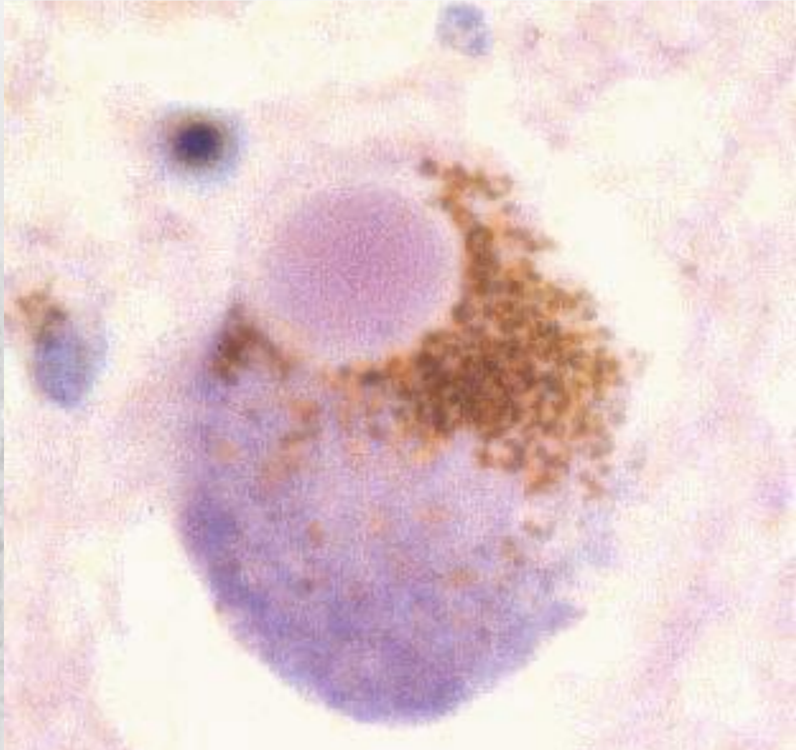
Pathology of Parkinson's Disease



- Cell degeneration and loss of pigmented neurones in the pars compacta of the substantia nigra as shown in this transverse section through the midbrain, where one can see quite marked macroscopic depigmentation compared to normal brain tissue.

Pathology of Parkinson’s Disease

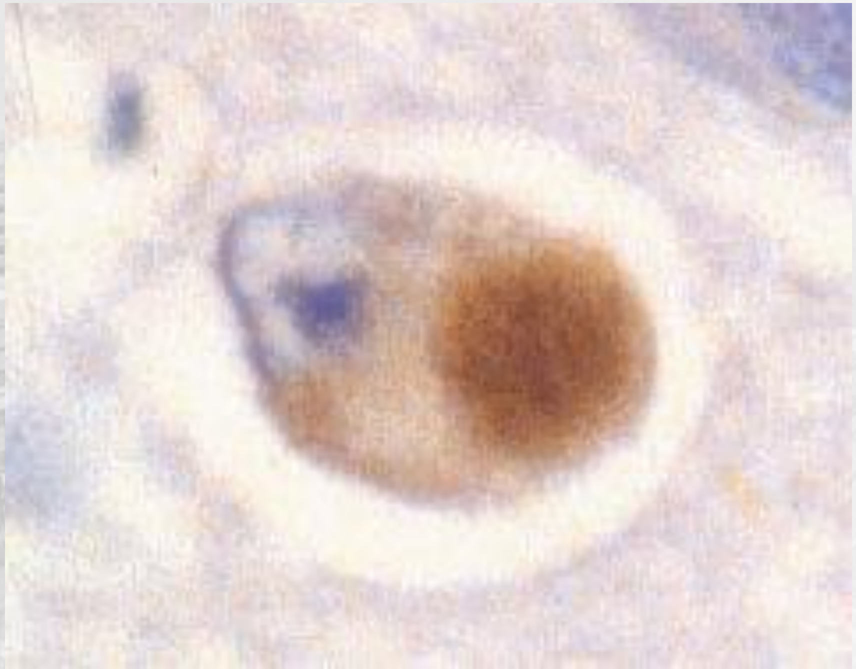
- **Microscopically, there is gliosis and pigment granules may be found extracellularly, leading to uptake within macrophages. Other neurones contain cytoplasmic inclusion bodies called Lewy bodies.**



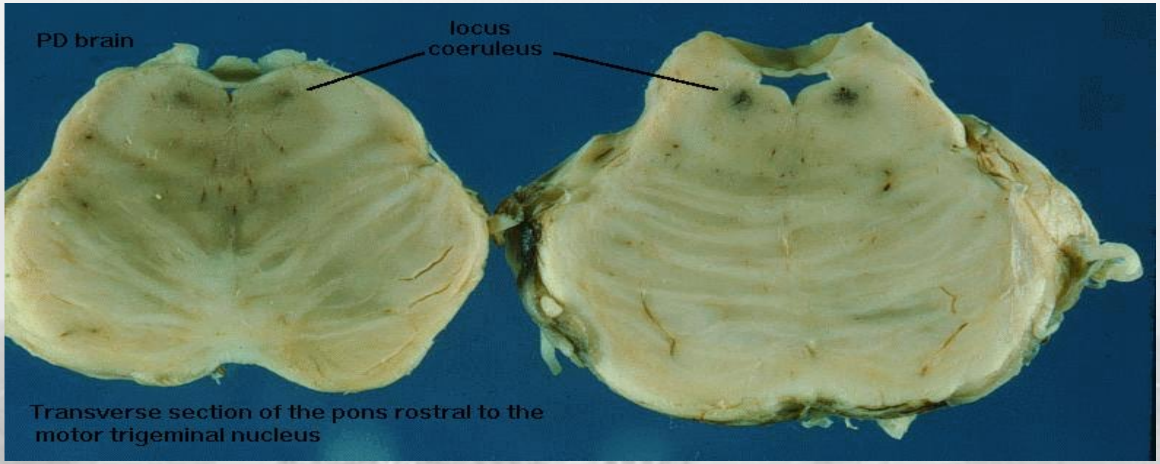
Lewy bodies in a neuron from the substantia nigra in PD

Pathology of Parkinson's Disease

- Their precise origin is uncertain, but they are characterised by an eosinophilic core surrounded by a clear halo. They contain accumulations of normal neurofilament and stain positively with ubiquitin, a protein involved in proteolysis.



Pathology of Parkinson's Disease



- Lewy bodies are found in other parts of the brain, including the substantia innominata, the intermediolateral cell column of the spinal cord, the locus coeruleus, the dorsal motor nucleus of the vagus nerve, and the cerebral cortex.

Pathology of Parkinson's Disease

- **Although believed to be highly sensitive markers for PD, they are not fully specific, e.g. diffuse cortical (Lewy-body) disease with dementia.**

Pathology of Parkinson’s Disease

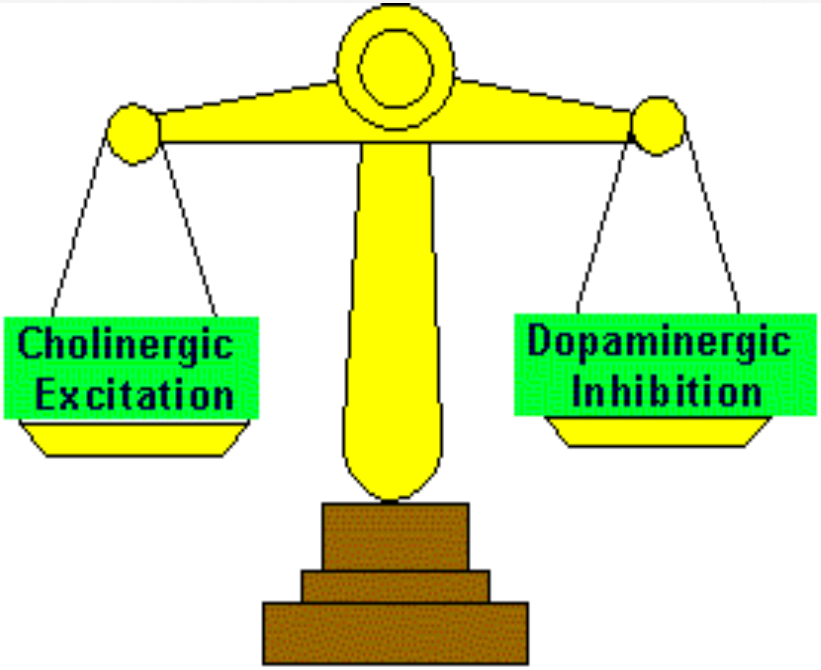
- **Approximately 60 per cent of nigral neurones have to be lost, with an 80 per cent depletion of striatal dopamine, before the symptoms of PD develop.**

巴金森氏病的治療方法

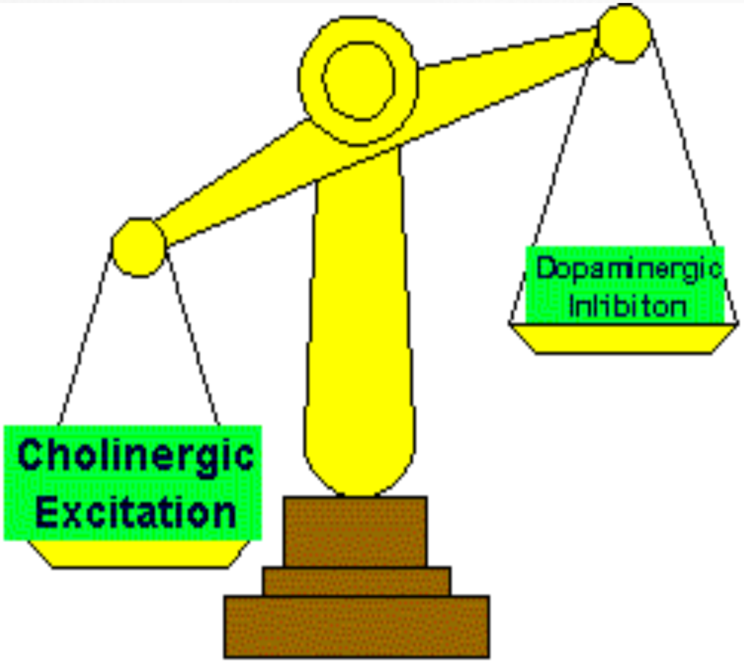
- 巴金森氏病的內科治療
  - 藥物治療
  - 營養需求
  - 心理建設
- 巴金森氏病的外科治療
- 巴金森氏病的復健治療

Milestones in the History of the Treatment of Parkinson's Disease

1867	Ordenstein	Belladonna alkaloid, an anticholinergic, is effective
1877	Charcot	
1949	Dorshay	Benztropine mesylate
1949	Corbin	Trihexylphenidyl
1960	Birkmayer et al.	First attempt to administer Levodpa
1967	Cotzias	Low dosages of levodopa, gradually increased, are tolerated and efficacious



Condition in the Normal Brain



Condition in the Parkinson Brain

Loss of Dopaminergic Cells in Substantia Nigra
Loss of Dopaminergic Inhibition in the Target Area (Striatum)
Cholinergic Excitation
Reversal of Disease Symptoms
Parkinson's Disease
Anticholinergics
L-Dopa+Carbidopa
Amantadine
MAO Inhibitors
Bromocriptine
Rx
Pharmacological Management
Transplantation Therapy

Drug Treatment for PD

- **Levodopa**
- **Dopamine agonists**
- **MAO-B Inhibitor (Selegiline)**
- **Anticholinergics**
- **Amantadine**
- **COMT Inhibitors (Tolcapone or Entacapone)**

巴金森氏病的藥物治療

- 左多巴Levodopa
- 多巴胺促效劑 (Dopamine agonists)
- MAO-B抑制劑 (Selegiline)
- 抗膽激素(Anticholinergics)
- 多巴胺放出促進藥(Amantadine HCL)
- COMT 抑制劑 (Tolcapone 或Entacapone)

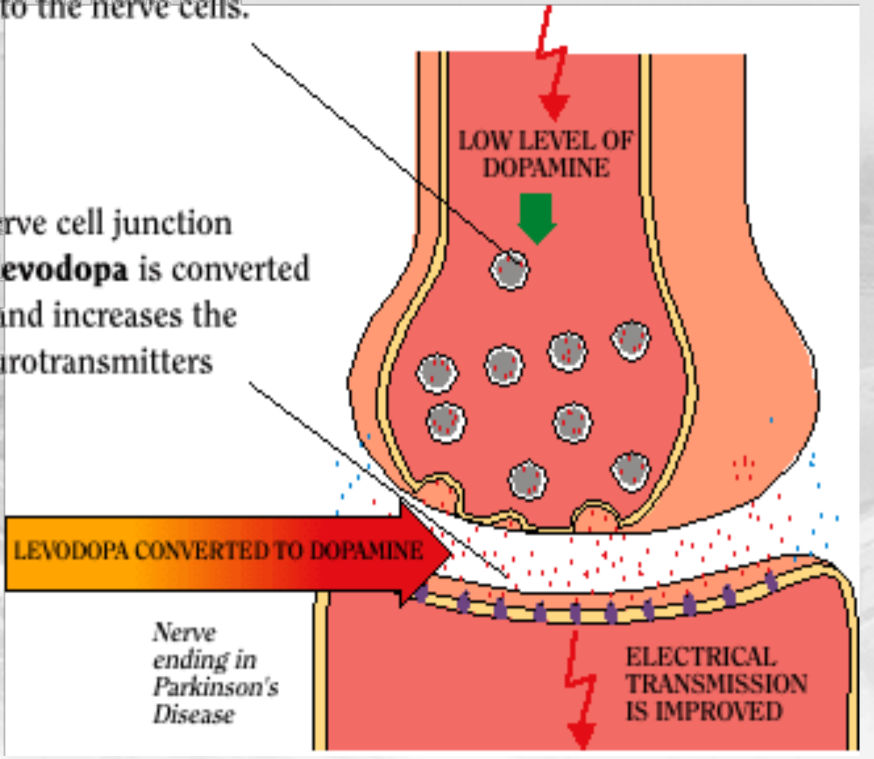
左多巴Levodopa

- 名稱：Madopar, Sinemet
- 作用：最有效，最常用的藥物；簡單而且直接地補充腦內不足的多巴胺。左多巴可以進入腦內轉化成多巴胺以補充失去的多巴胺。為了防止左多巴在進入大腦內之前就被多巴脫羧酵素(dopa decarboxylase) 轉化成多巴胺，左多巴通常加入抑制劑Benzerazide (Madopar)或Carbidopa (Sinemet)來阻擾多巴脫羧酵素的作用。這藥品在初期都是少量使用，再慢慢增加劑量；這樣可以控制副作用, 並延長使用期間。

Levodopa

LEVODOPA is rapidly absorbed from the small intestine and passes into the bloodstream. Some of the drug is broken down in the blood, and at other sites in the body, leaving a percentage which is transported to the brain (crossing the blood/brain barrier) and into the nerve cells.

At the brain nerve cell junction (synapse) the **levodopa** is converted to **dopamine** and increases the quantity of neurotransmitters released.



Levodopa

- **Example: Sinemet, Madopar**
- **Since dopamine does not cross the blood brain barrier, but its precursor Levodopa does, L-Dopa is given in an effort to replace the striatal dopamine deficiency. However, since L-dopa has significant peripheral metabolism, resulting in untoward side effects (nausea and vomiting) and decreased brain delivery of L-dopa, it is combined with a peripheral decarboxylase inhibitor.**

Levodopa

Levodopa/Carbidopa (Sinemet) / Levodopa/Benserazide (Prolopa)

- **Patients gain reasonably good control of their Parkinson's disabilities for about 5 years**
- **Crosses the blood-brain barrier and is converted to dopamine**
- **Most common side effects**
  - **Buccal dyskinesia, oculogyric crises**
  - **Vivid dreams**
  - **Nausea, vomiting, orthostatic hypotension for 1st 2-3 months**

Levodopa

Levodopa/Carbidopa (Sinemet) / Levodopa/Benserazide (Prolopa)

- **Long term side effects are caused by progressive loss of dopamine neurons**
- **ON-OFF as drug wears off - smaller doses recommended**
  - **Freezing episodes**
  - **End of dose deterioration**
  - **Dyskinesia (unwanted movements) at beginning of dose**
- **Name of enzyme: L-dopa decarboxylase**
- **3% crosses blood-brain barrier**

Levodopa

Side effects:

- nausea or vomiting
- postural hypotension
- worsening of peptic ulcer symptoms
- sweating
- discoloration of urine/sweat

SIDE EFFECTS OF LEVODOPA

- Gastrointestinal
  - Anorexia, Nausea, Vomiting
- Cardiovascular
  - Cardiac arrhythmia
  - Orthostatic hypotension
- Psychiatric
  - Mood disorders (euphoria, depression)
  - Increased libido
  - Sleep disorders (diurnal somnolence, insomnia, sleep fragmentation, vivid dreams, nightmares, nocturnal myoclonus)
  - Dopa-induced psychosis (hallucinations, paranoid delusions)
- Motor
  - Response fluctuations
  - Dyskinesias

Levodopa

Problems of long-term use:

- **Motor fluctuations and dyskinesias. These probably represent the biggest single problem in the long-term management of a patient with Parkinson's disease. It is estimated that at least 50% of patients with Parkinson's develop these complications within the first 5 years of treatment.**
- **Neuropsychiatric problems. Confusion, hallucinations, psychosis.**

左多巴Levodopa

- 優點：大部分患者都能接受Madopar和Sinemet 的療效；而在幾年中有明顯的進步，尤其是對肌肉僵化以及行動緩慢的問題。
- 缺點：患者普遍會感覺到便秘、反胃、及不自主動作的副作用。另有些患者會有起立性低血壓、幻覺、情緒不穩、昏睡、或精神狀態轉變等困擾。這些副作用通常是和病情的發展有關，而和藥物無關。一般服用五年後，有75% 的人藥效會減少，而且患者行動中會有突然從來電變成斷電(不能行動)一的情形。如果服用劑量的改變不能解決這問題，患者可能要嘗試其他藥物來配合。

左多巴藥的效用

可以減輕下列巴金森病的主要症狀：

- 行動緩慢
- 僵硬
- 顫抖
- 走路不平衡
- 臉上沒有表情
- 寫字字體扭曲變小

左多巴藥的效用

對於以下的症狀並不一定有效：

- 姿勢不平衡
- 言語困難
- 性能力失衡
- 流汗過多
- 神經感覺的問題：疼痛和麻痺等
- 油性皮膚
- 便秘
- 憂鬱
- 癡呆

Symptoms Unresponsive to Levodopa

- **Postural instability**
- **Freezing**
- **Speech abnormalities**
- **Mental changes**
  - **Dementia**
  - **Depression**
- **Sleep disturbances**
- **Dysautonomia**
  - **Constiaption**
  - **Sexual dysfunction**
  - **Bladder dysfunction**
  - **Sweating**
- **Sensory phenomenon**

DRUG INTERACTIONS WITH LEVODOPA

Drug	*Mechanism of Action*
Neuroleptics	Dopamine (DA) receptor blockade
Benzamides: metoclopramide, sulpiride, etc.	Dopamine receptor blockade a
Calcium channel blocker: flunarizine, nifedipine, etc	DA release inhibition; DA receptor blockade
Alpha-methyl-dopa	Competition for substrate
Fluoxetine	Serotonin/DA interaction
Isoniazid	Central inhibition of dopa-decarboxylase
Monoamine oxidase A inhibitors	Interaction with tyramine
Rserpine, tetrabenazine	DA depletion
Dietary amino acids	Competition for transport
Anticholinergic	Delayed gastric emptying

Dopamine Agonists

- **Examples: Bromocriptine; Pergolide; Lisuride. (Pramipexole, Ropinirole, Apormorphine)**
- **These 3 drugs vary both in their duration of action and the degree to which they are D1 or D2 agonists. Thus:**
  Lisuride - short duration of action, mainly a D2 agonist
- **Pergolide- longest duration of action, acts on both D1 and D2 receptors.**

Dopamine Agonists

Bromocriptine (Parlodel) / Pergolide (Permax)

- Readily cross the blood-brain barrier and act directly on striatal post-synaptic dopamine receptors
- Longer duration of action compared to levodopa
- Most common side effects
  - Parlodel: Nausea, vomiting, headache and gastrointestinal problems
  - Permax: Nervous system, blurred vision, nausea and nervousness
- Permax has a longer duration of action than Parlodel
- Smoothen L-dopa peaks and troughs with dopamine agonists
- May have protective effect
- Glutamate agonists
  - Aim is to reduce subthalmic overactivity

Dopamine Receptors

Receptor Type	D1	D2	D3	D4	D5
Human chromosome	5	11	3	11	4
cAMP	↑	↓	↓?	↓?	↑
mRNA distribution	striatum nucleus accumbens, olfactory tubercle		hypoth	frontal cortex midbrain medulla	hypoth hippoc

Hypoth, hypothalamus; hippoc, hippocampus

Dopamine Agonists

DA agonists	D1	D2	D3	D4	D5
Dopamine	+	++	+++	++	+++
Bromocriptine	-	++	+	+	+
Pergolide	+	+++	+++	+++	+
Pramipexole	-	+++	++++	++	-
Ropinirole	-	+++	++	-	-

DOPAMINE AGONISTS

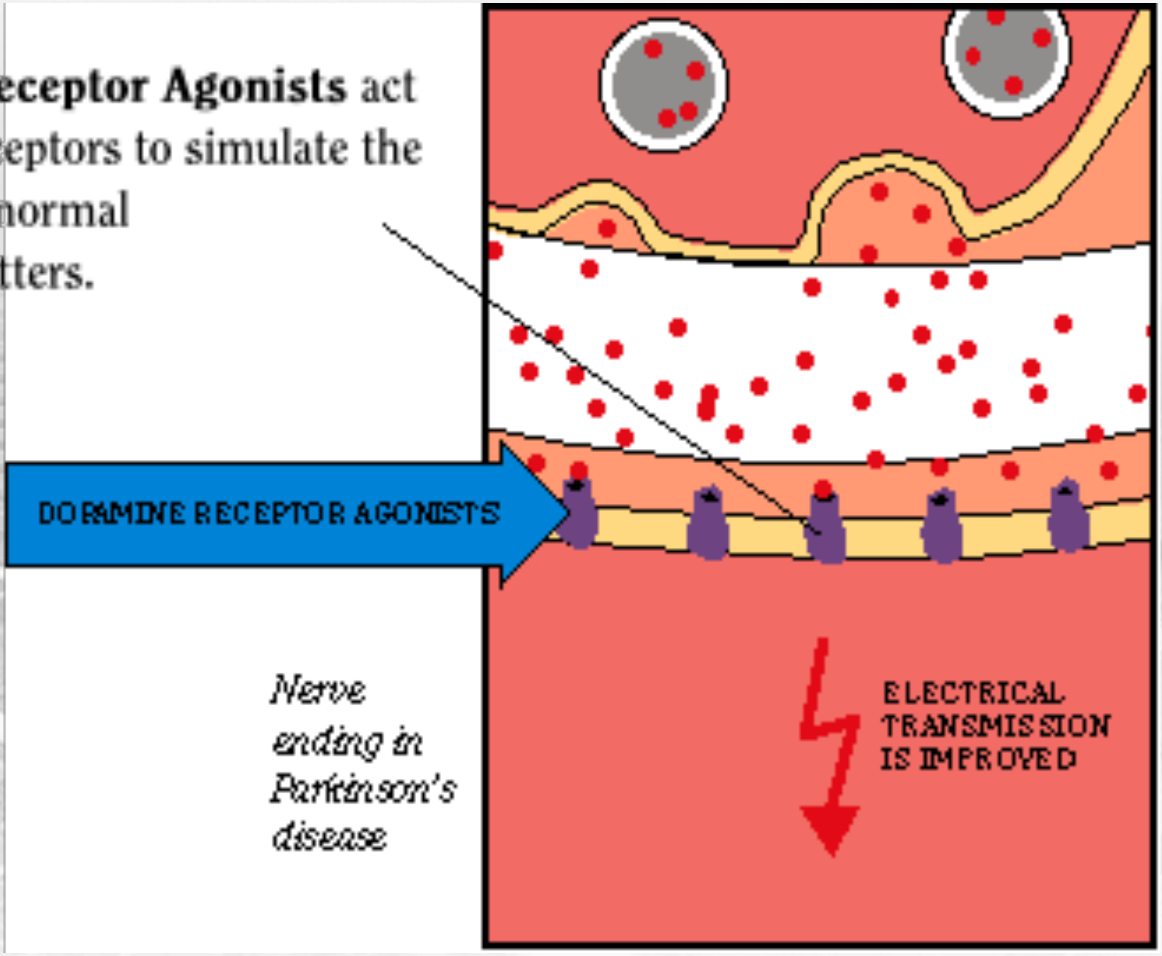
Generic Name	Dopamine-Receptor Profile	Daily Dose (mg)
Bromocriptine	D2	7.5-45.0
Pergolide	D1, D2	1.5-4.0
Lisuride	D2	1.5-4.5
Pramipexole	D2, D3	3-4
Ropinirole	D2, D3	6-8
Apomorphine	D1, D2	2-100

多巴胺促效劑 (Dopa-agonists)

- 名稱：**Parlodel, Celance, Revanil, Permax, Requip, Mirapex, Destinex**
- 作用：多巴胺促效劑的結構類似多巴胺，它不用經過腦細胞轉化，直接刺激大腦內的多巴胺受容器 (Dopamine receptor)，以代替腦部分泌不足的多巴胺。

DOPAMINE RECEPTOR AGONISTS may be used as adjuvant therapy when ledodopa does not adequately control the symptoms of when there are severe side-effects of levodopa such as “on-off” effects (periods with/without symptoms) Some dopamine agonists are used on their own in the early stages.

Dopamine Receptor Agonists act on the cell receptors to simulate the effects of the normal neurotransmitters.



Dopamine Agonists

- There is evidence that patients who can tolerate monotherapy with a dopamine agonist for a prolonged time that the incidence of dyskinesias and motor fluctuations in the long term is reduced. The downside of this is that the dose needs to be gradually increased very slowly and side effects are more common than L-dopa.
- These act directly on the dopamine D1 and D2 receptors. Since they also act in the periphery on the dopamine receptors of the vomiting centre, they can also cause nausea and vomiting.

多巴胺促效劑 (Dopamine agonists)

- 優點：這種藥比左多巴藥能較長期地控制症狀，而且較不會受斷電及不自主動作的左多巴副作用的影響。此藥還可以減少Sinemet 和 Madopar的用量。
- 缺點：這藥單獨使用時，比任何一種Levodopa (Mardopa 和Sinemet) 有更多的副作用。有些患者因為反胃、昏睡、迷惑、幻覺、不自主動作、及低血壓等副作用而不能繼續服用。有些患者在服用後會影響肺部而感到呼吸短促或咳嗽，這問題要馬上知醫生。這在開處方前可先照胸部 X 光加以預防。

Advantages of Dopamine Agonists

Pharmacologic advantages

1. Directly stimulate DA receptors, bypassing degenerating nigrostriatal neurons
2. Do not require enzymatic conversion
3. Longer striatal half-life than levodopa
4. Do not compete for transport in the gut or at the blood-brain barrier
5. Selective receptor activation may be possible
6. Alternative routes of administration may be possible (lisuride, apormorphine, N-0923)

Possible protective effects (reduce oxidative stress)

Advantages of Dopamine Agonists

Pharmacologic advantages

Possible protective effects (reduce oxidative stress)

1. **Do not generate free radicals or potentially toxic products**
2. **May decrease presynaptic DA turnover**
3. **Delay levodopa initiation and side effects**

Disadvantages of Dopamine Agonists

1. Less effective than levodopa in reducing Parkinson's symptoms
2. More adverse effects:
   - Psychiatric phenomenon, orthostatic hypotension, peptic ulcer, vasoconstrictive effects, erythromelalgia, pulmonary effects, and retroperitoneal fibrosis
3. More down-regulation of receptors
4. Higher cost

Dopamine Agonists

Side effects:

- nausea or vomiting
- postural hypotension
- neuropsychiatric side effects (as for L-dopa but occur more frequently)
- vasospasm
- ankle swelling
- retroperitoneal fibrosis (rare)

SIDE EFFECTS OF DOPAMINE AGONISTS

- Gastrointestinal
  - Nausea and vomiting
- Cardiovascular
  - Orthostatic hypotension; Cardiac arrhythmia; Digital vasospasm
- Pulmonary
  - Pleural fibrosis
- Psychiatric
  - Sedation; Dopaminomimetic psychosis
- Other
  - Headache; Nasal congestion; Erythromelalgia; Retroperitoneal fibrosis

Dopamine Agonists

Apomorphine

- Apomorphine is also a D1 and D2 agonist, but since it is given parentally via subcutaneous injection, its use is generally witheld until problems with motor fluctuations and 'on-off' fluctuations occur which are not being easily controlled via other drugs. As a result of this, initiation of therapy is best instituted in the context of a specialist Parkinson's clinic.

Apormophine

Side effects:

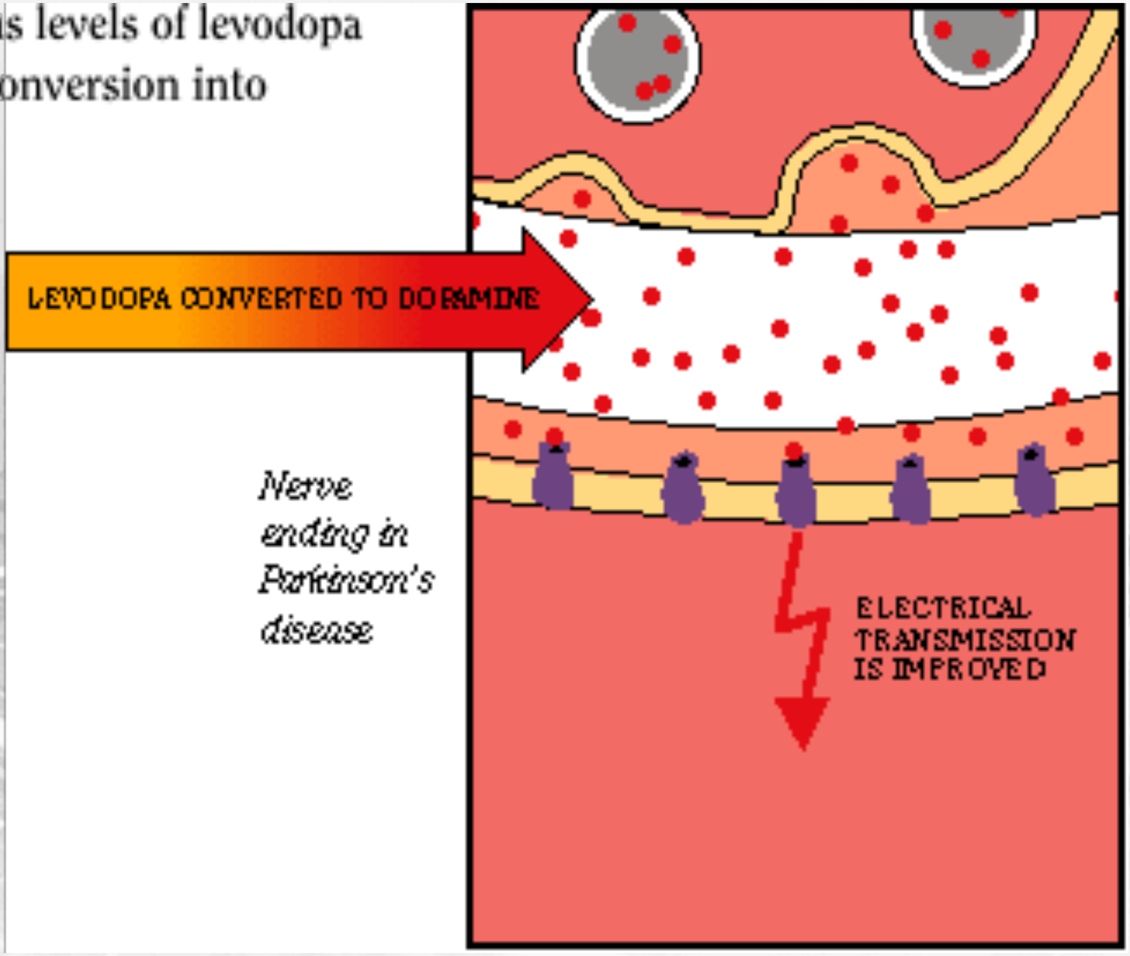
- **nausea or vomiting.-on account of this, the patient needs to be given Domperidone as an anti-emetic prior to the use of Apomorphine.**
- **postural hypotension**
- **sweating**
- **yawning**
- **drowsiness**
- **local skin reactions at injection site**
- **motor fluctuations and dyskinesias**
- **confusion and hallucinations**

MAO-B抑制劑 (Selegiline)

- 名稱：Jumexal, Deprenyl, Eldepryl, Zelapar
- 作用：它能夠阻礙大腦中的多巴胺被B型單胺氧化酵素(Monoamine Oxidase-B, MAO-B)分解而增加左多巴所能夠產生的多巴胺。因此它可以用來延長使用Madopar 和 Sinemet的效期或減少劑量。抑制MAO-B同時也可能延緩巴金森病的進行。

MAOIs slow the breakdown of levodopa in the brain. They act upon the Monoamine-B

This maintains levels of levodopa available for conversion into dopamine



MAO-B抑制劑 (Selegiline)

- 優點：過了最初的適應期，藥物的副作用會變得十分少，而藥效會和Madopar 及 Sinemet 相似。
- 缺點：這藥因為是加強左多巴的功效，所以可能加深Madopar 和 Sinemet的便秘、行動困難、迷惑、血壓降低、和幻覺等副作用。Deprenyl對心絞痛及消化性潰瘍出血的患者不能使用。這藥也是一輕微興奮劑，所以患者只適合在上午服用；晚上服用常會影響睡眠。

Selegiline (Deprenyl)

- Selegiline is a selective inhibitor of monoamine oxidase type B which metabolises dopamine.
- There was considerable interest in the use of Selegiline as a neuroprotective agent given the results of the DATATOP study (NEJM 1989;321:1364-1371). However, there has been considerable controversy over the interpretation of the results of this and other studies in that was Selegiline truly neuroprotective or does it have some kind of symptomatic effect. Most neurologists now tend to favour the latter.
  Secondly, there has been some suggestion that the use of Selegiline is associated with increased mortality (BMJ 1995;311:1602-1607). This has been shown in one study, however, the causes of death are unknown at present. Nonetheless it would seem to lay to rest the neuroprotective argument for Selegiline. Since we do not have data from any other studies or details on the causes of death in the Selegiline group in the BMJ paper, at present we do not know whether the reported increased mortality in the BMJ paper is causally linked with Selegiline or not.

Selegiline and Rasagiline

- Delays Parkinsonian disability and the need for levodopa therapy by 9-12 months
- Inhibits dopamine degradation
- allows for 20% smaller doses of levodopa
- reduces adverse effects
- Most common side effects
- Exacerbation of levodopa-associated side effects
- Insomnia, postural hypotension

Selegiline

Selegiline Hydrochloride (Deprenyl, Eldepryl)

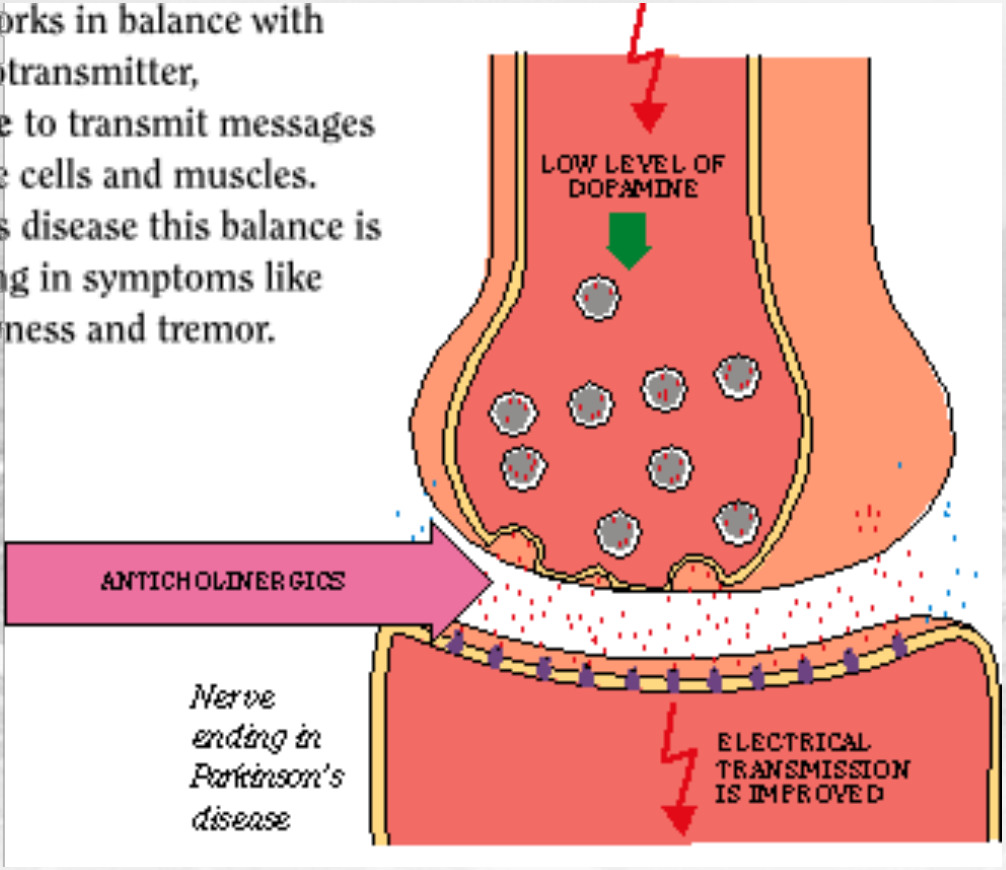
- Selegiline works by inhibiting monoamine oxidase-B and prevents oxidation of the pre-synaptic dopamine
- This increases the concentration of the synaptic dopamine, and may explain the symptomatic effect of the drug
- May cause insomnia, therefore given at lunch, not dinner
- Interacts with Prozac

抗膽激素(Anticholinergics)

- 名稱： **Artane, Akineton, Cogentin, Kemadrin, Disipal, Benzhexol**
- 作用：抗膽激素是一百年前發現的巴金森病藥物。它被用來阻擾化學神經傳導媒–乙醯膽素(**Acetychloline**)的作用，以維持和多巴胺的平衡。可以抑制顫抖，肌肉僵硬、加強對肌肉的控制；並延後使用左多巴藥的時間。

ANTICHOLINERGICS inhibit the action of acetylcholine at the synapse which relieves some of the symptoms

Dopamine works in balance with another neurotransmitter, **acetylcholine** to transmit messages between nerve cells and muscles.
In Parkinson's disease this balance is upset, resulting in symptoms like stiffness, slowness and tremor.



Anticholinergics

- Example: Artane, Akineton, Cogentin, Kemadrin, Disipal, Benzhexol
- These drugs have a mild antiparkinsonian effect and are said to be more effective for tremor. These drugs should always be stopped slowly to avoid a rebound worsening of Parkinsonian symptoms.

Anticholinergics

Potential side effects:

- Neuropsychiatric
  Visual hallucinations, poor concentration/memory, organic confusional state.
  Patients with dementia or the elderly are particularly prone to developing these sorts of problems with anticholinergics.
- Blurred near vision
  due to mydriasis. Therefore these drugs are contraindicated in narrow-angle glaucoma.
- Dry mouth
- Acute urinary retention in males with prostatic enlargement
- Constipation
- Dyskinesia

抗膽激素(Anticholinergics)

- 優點：對患病初期、病情較輕的年輕患者較有效。
- 缺點：這些藥物有口乾、噁心、便秘、小便失禁、視力模糊、失憶、錯亂、心悸、失眠等副作用。由於己有其他藥物可取代，這藥物現在較少使用。這藥通常不會開給七十五歲以上的患者使用。

Anticholinergics

- **Prescribed for control of tremor and rigidity**
- **Blocks acetylcholine receptors**
- **Most common side effects**
- **Dry mouth, blurred vision, nausea, nervousness, dizziness, confusion, constipation, urinary retention**
- **Delays gastric emptying (allows for levodopa absorption)**

多巴胺放出促進藥(Amantadine HCL)

- 名稱：PK-Merz, Symmetrel, Endstadine
- 作用：Amantadine是治療流行性感冒被意外發現的藥。它有助於增加大腦部分泌的多巴胺、使多巴胺在其作用的地方停留較久而不會為其他細胞所用；因而舒緩巴金森症病情，並延後使用左多巴藥的時間。

Amantadine

- **This is a mild antiparkinsonian drug . The dose should be reduced with renal impairment.**

Side effects:

- **livedo reticularis**
- **ankle oedema**
- **confusion**

多巴胺放出促進藥(Amantadine HCL)

- 優點：副作用較不嚴重；可以用來控制患者身體的震顫。
- 缺點：這些藥物有起疹子、腳踝關節腫大、腳部膚色改變、迷惑、沮喪、昏睡等副作用。而且效用輕微而短暫，有心臟病及腎衰竭的患者不能使用。只能幫助小部分患者。

Amantadine

(PK-Merz, Endantamine)

- **Modest improvements for about one year, at which point levodopa becomes necessary**
- **Enhances levodopa release from, and inhibits re-uptake into presynaptic storage vesicles**
- **Most common side effects**
  - **Nausea, dizziness and insomnia**
  - **Increase incidence of seizures, orthostatic hypotension**
  - **Mild anticholinergic effects**

SIDE EFFECTS OF ANTICHOLINERGICS AND AMANTADINE

- **Anticholinergics**
  - Blurred vision
  - Constipation
  - Urinary retention
  - Memory impairment
  - Cognitive deterioration
  - Confusion
  - Delirium
- **Amantadine**
  - All of the above
  - 0Livedo reticularis

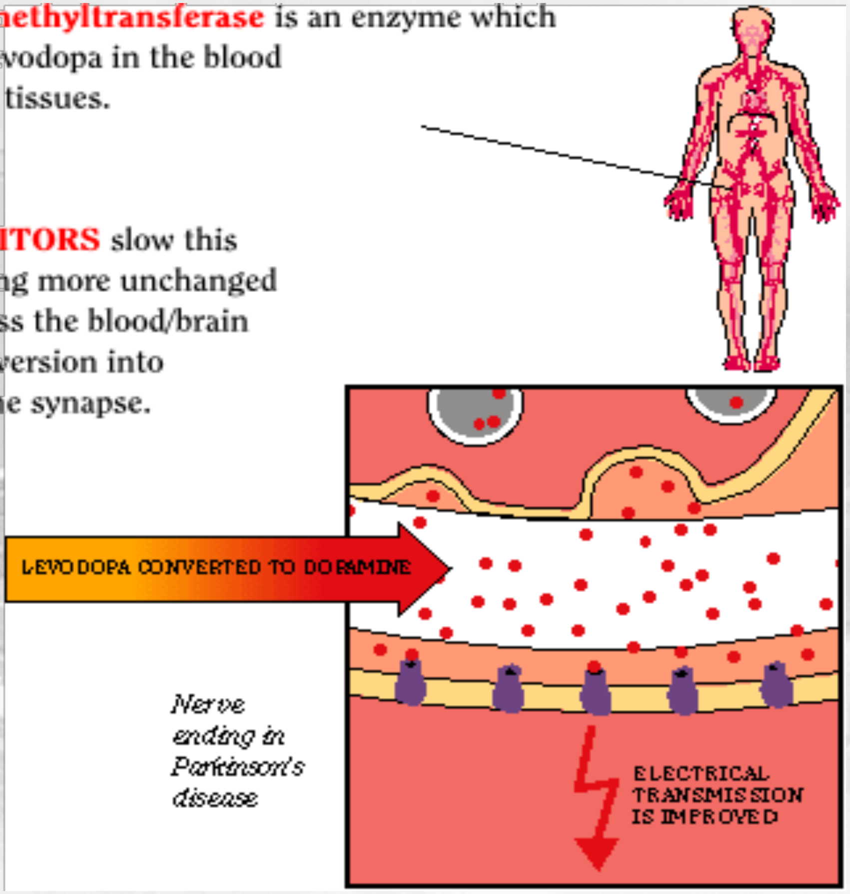
COMT 抑制劑 (Tolcapone 或Entacapone)

- 名稱：答是美Tasmar
- 作用：它利用抑制腦內的兒茶酚氧位甲基轉移酵素(Catechol-O-Methyl Transferase, COMT)以阻礙左多巴被分解；增加並延長多巴胺的數量和效用。

COMT Inhibitors

Catechol-O-methyltransferase is an enzyme which breaks down levodopa in the blood and peripheral tissues.

COMT INHIBITORS slow this process enabling more unchanged levodopa to pass the blood/brain barrier for conversion into dopamine at the synapse.



COMT Inhibitors

Examples: Tolcapone, Entacapone

- These are relatively new drugs. They are COMT inhibitors (catechol-O-methyltransferase inhibitors) and as such slow down break down of L-dopa either in the periphery alone (Entacapone) or centrally as well (Tolcapone). Results from studies suggest that they have a role in reducing on-off fluctuations and dyskinesias. Trial have shown alterations in liver function tests (LFTs), the exact mechanism for this is unknown, but for the first 6 months, LFTs need to be checked. Some patients develop diarrhoea but this is reversible. The main problems with COMT inhibitors are worsening of peak-dose dyskinesias, but it is relatively easy to treat this by reducing the amount of L-dopa.

COMT 抑制劑 (Tolcapone 或Entacapone)

- 優點：減少因長期使用Sinemet而產生的斷電效應和不自主運動的副作用。
- 缺點：這藥物有腹瀉、反胃、和行動困難的副作用可能影響肝功能。

Starlevo

= **Levodopa + Carbidopa + Entacapone**

= **Sinemet + Entacapone**

Side Effects of Levodopa

- **Peripheral and medullary emetic center**
  - **Nausea, vomiting, anorexia**
  - **Orthostatic hypotension**
- **Central**
  - **Chorea**
  - **Dystonia[a]**
  - **Myoclonus**
  - **Akathisia[a]**
  - **Hallucinations[a]**

[a]May not be related to levodopa therapy

Side Effects of Levodopa

Peripheral and Medullary Emetic Center	Management
Nausea, vomiting, anorexia	A. Carbidopa B. Diphenidol, hydroxyzine, cyclizine C. Ondansetron D. Domperidone
Orthostatic hypotension	A. Carbidopa B. Fluorinef, NaCl C. Midodrine D. Elastic stocking

Side Effects of Levodopa

Central	Management
Chorea	A. Reduce levodopa B. Reduce anticholinergics C. Amantadine D. Yohimbine E. Glutamate antagonists F. Surgery

Side Effects of Levodopa

Central	Management
Dystonia	A. Reduce levodopa; (increase dose in D-I-D) B. Sinemet™ CR, mardopar HBS C. Anticholinergics D. Tricyclics E. Baclofen, tizanidine, mexilitine F. DA agonists G. Lithium H. Botulinum toxin I. Surgery

Side Effects of Levodopa

Central	Management
Myoclonus	A. Reduce levodopa B. Clonazepam C. Valproate

Side Effects of Levodopa

Central	Management
Akathisia	A. Anxiolytics
	B. Propranolol
	C. Naltrexone

Side Effects of Levodopa

Central	Management
Hallucinations	A. Reduce levodopa B. Clozapine C. Ondasetron D. Olanzapine E. Drug holiday

LONG-TERM COMPLICATIONS OF LEVODOPA TREATMENT

- ***Response fluctuations***
  - **Wearing-off effect or end-of-dose deterioration**
  - **Early morning or nocturnal akinesia**
  - **Delayed on**
  - **On-off**
  - **Drug-resistant off periods**
- ***Dyskinesias***
  - **Peak-dose or benefit-of-dose dyskinesias, usually choreic in nature**
  - **Diphasic dyskinesias, usually dystonic, ballisitc, or repetitive, often involving the lower extremities**
  - **Off-period dyskinesias, usually dystonic in nature**

PSYCHIATRIC DISTURBANCES AFTER LONG-TERM LEVODOPA TREATMENT

- Illusions or pseudohallucinations
- Visual hallucinations
- Paranoid delusions
- Confusional state
- Dopaminomimetic psychosis

Pharmacological Management of Other Movement Disorders

Pharmacological Management of Other Movement Disorders

- **Tremor**
  - Propranolol
- **Chorea**
  - Haloperidol
- **Dystonia**
  - Botulinum toxin injection
- **Myoclonus**
    - Clonazepam, Valproate, Piracetam,

Tremor

Easily Seen but Difficult to Describe and Treat

Tremor

- **Tremor is the rhythmical, involuntary oscillatory movement of a body part. The terminology for describing tremor is often confusing, with authors using different terminology to describe the same tremor. Below is a summary of the phenomenology and a syndromic classification of tremor from a consensus statement from the Movement Disorder Society published in 1998. Modifications of this approach will occur but it does provide a framework from which to build.**